THE ROLE OF EXECUTIVE FUNCTIONING IN RISK FOR DEPRESSION: A MULTI-METHOD LONGITUDINAL INVESTIGATION

BY

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DISSERTATION

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ABSTRACT

Broad deficits in executive function (EF) are a common finding in clinical depression. Previously considered to be the result of depression, impaired EF is increasingly recognized as a risk factor that has implications for the onset and course of depression. While the developmental literature indicates that EF deficits prospectively predict future depression, prospective work with adults has been limited. The present studies prospectively assessed whether EF deficits predict future depressive symptoms using multiple measures of EF. Study 1 examined relationships between self-reported EF deficits, a task-based measure of updating working memory (WM), and current and future depressive symptoms among adults who were not selected for psychopathology risk. Study 2 examined relationships among self-reported EF deficits, task-based measures of inhibition, shifting, and updating WM, neural activity during an fMRI task that assessed inhibitory functioning, and current and future depressive symptoms among adults who were selected for psychopathology risk. Study 1 found that broad self-reported EF deficits and the task-based measure of updating WM predicted current and future depressive symptoms, although only self-reported shifting predicted future depressive symptoms after controlling for baseline symptoms of depression and anxiety. Study 2 found that broad self-reported EF predicted current and future depressive symptoms, though only self-reported inhibition and WM predicted future depressive symptoms after controlling for baseline symptoms of depression and anxiety. Only task-based inhibition predicted current depressive symptoms, whereas updating WM and a general measure of EF predicted future depressive symptoms. Furthermore, aberrant neural activity for positive stimuli during the fMRI task predicted future depressive symptoms. Results indicate that, among adults, EF deficits confer risk for future depression.

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TABLE OF CONTENTS

CHAPTER 1: GENERAL INTRODUCTION

Although depression has been identified as a leading cause of disability worldwide for over 20 years, it was recently upgraded to the leading cause of disability according to the World Health Organization (2017). Not only is depression impairing, it is one of the most prevalent mental health disorders, with approximately 20 percent of Americans experiencing depression in their lifetime (Kessler et al., 2003) and an estimated 300 million people worldwide suffering from depression (World Health Organization, 2017). Furthermore, it has one of the highest costs of any disorder, with an economic burden that has been rising substantially in America since 2000. Its costs have reportedly jumped from 87 billion dollars in 2000, to 173 billion dollars in 2005, and to 210 billion dollars in 2010 (Greenberg et al., 2003, 2015). In other countries, the economic burden is also prominent, with an estimated impact of 118 billion dollars in Europe in 2004 alone (Sobocki, Jönsson, Angst, & Rehnberg, 2006).

The profound impact of this disorder is reflected not only in its economic costs, but in the many challenges and impairments experienced by individuals with depression across multiple life domains, including physical health, social and family relationships, work, and daily life (Rappaport, Clary, Fayyad, & Endicott, 2005). This impact is well-captured in first-hand accounts, such as those by Andrew Solomon and William Styron, in which depression has been described as a "storm of murk" characterized by unrelenting pain, loss of physical and mental energy, and an overwhelming sense of hopelessness that "crushes the soul" (Styron, 1990).

One aspect of depression that is reported to be of critical importance is its impact on cognitive functioning (Levin et al., 2007). One of the hallmarks of depression is an impaired ability to think, which is captured by the "diminished ability to think or concentrate" criterion of clinical depression (American Psychiatric Association, 2013). It has been argued that deficits in

executive function (EF) may is the basis for many of the cognitive deficits seen in depression (Levin et al., 2007). Thus, depression may impact EF, and in turn this disruption may account for the cognitive deficits in memory and attention associated with depression.

Broadly, impairments in EF have been reported among individuals with depression in numerous studies (Austin, Mitchell, & Goodwin, 2001; Castaneda et al., 2008; Dichter, Felder, & Smoski, 2009; Heinzel, Northoff, Boeker, Boesiger, & Grimm, 2010; Murrough, Iacoviello, Neumeister, Charney, & Iosifescu, 2011; Rock, Roiser, Riedel, & Blackwell, 2014; Rogers et al., 2004; Snyder, 2013; Vasic, Walter, Sambataro, & Wolf, 2009). EF is an umbrella term for cognitive processes that help individuals formulate goals and guide their behavior toward achieving goals, especially in novel situations (Alvarez & Emory, 2006; Banich, 2009; Lezak, 1982). These processes generally require more effort to implement than other more automatic cognitive processes (e.g., the startle response), which are influenced more by sensory stimuli than internal states (Miller & Cohen, 2001). More narrowly, EF is also sometimes referred to as "cognitive control" (e.g., Miller & Cohen, 2001).

There are different theories regarding the nature of EF and what components fall under the EF umbrella. For example, one view purports that EF is comprised of both a common or general EF and specific EF components which is best captured by a bi-factor model (Miyake & Friedman, 2012; Friedman & Miyake, 2017). Another view, captured by the dual mechanisms of control model, emphasizes that EF is comprised of proactive and reactive control functions that allow individuals to exert flexibility in goal-directed action (Braver, 2012; Braver, Paxton, Locke, & Barch, 2009). Yet another view, captured by the dual-networks model of cognitive control, purports that top-down control functions can be parsed into flexibility and set-maintenance functions that are implemented via two distinct control networks (Dosenbach, Fair,

Cohen, Schlaggar, & Petersen, 2008). Overall there is no consensus regarding which is the "best" model or conceptualization, and data do not unambiguously support one model over another (Karr et al., 2018). For example, whereas a two-factor solution characterized by maintenance and flexibility was the best fit for nine observed variables from EF tasks that were selected to asses multiple EFs (Niznikiewicz, 2015, unpublished master's thesis), a one-factor solution best fit nine different observed variables from tasks that were selected to measure the same EFs (Madian, Warren, Bredermeier, Miller, & Heller, in press). Madian et al. (in press) also found that a three-factor solution provided a good fit for the data, although the one-factor solution provided a more parsimonious fit.

Processes that have commonly been included in studies of EF include inhibition, shifting, and updating working memory (WM; Miyake et al., 2000). While Miyake et al. (2000) acknowledge that there are other EF components that are important to examine, they argue that inhibition, shifting, and updating WM are more circumscribed and less vaguely defined than other processes such as planning, which makes them prime targets for psychological research. It has been argued that the unity/diversity model, which includes inhibition, shifting, and updating WM, captures key components of EF and is particularly well-suited for determining which EF components are uniquely impacted by different forms of psychopathology (Snyder, Miyake, & Hankin, 2015). According to Miyake et al. (2000), inhibition is defined as the ability to override or prevent automatic or prepotent responses, shifting as the ability to flexibly switch between tasks and mental sets, and updating WM as the ability to revise information in WM by replacing no longer relevant information with updated information.

With regard to these specific aspects of EF, the impact of DSM-diagnosed depression has been examined for all of these domains using neuropsychological assessments (see Table 1, p.

60; for reviews, see Austin et al., 2001; Castaneda et al., 2008; Murrough et al., 2011; Rock et al., 2014; Rogers et al., 2004; Snyder, 2013). Despite some variation in individual studies, meta-analyses indicate that the effect of depression on impairment is moderate-to-large for inhibition (Stroop Interference RT, d = .39; Stroop Incongruence accuracy, d = .70; Snyder, 2013), shifting (Wisconsin Card Sorting task, d = .47; Trail Making B test, d = .59; Intradimensional/ Extradimensional Shift task, d = .46 and d = .44; Rock et al., 2014; Snyder, 2013), and updating WM (CANTAB Spatial WM, d = .54; Digit Span Backward, d = .55; Visuospatial Span Backward, d = .72; n-back task, d = .63; Rock et al., 2014; Snyder, 2013). Elevated levels of depressive symptoms in non-clinical samples have also been associated with EF deficits (Bredemeier, Warren, Berenbaum, Miller, & Heller, 2016; Letkiewicz et al., 2014).

fMRI studies have also revealed a meaningful relationship between EF and depression, with atypical neural activity occurring in multiple brain regions during EF tasks (Beevers, Clasen, Stice, & Schyner, 2010; Dichter et al., 2009; Engels et al., 2010; Heinzel, et al., 2010; Herrington et al., 2010; Siegle et al., 2007; Walter, Wolf, Spitzer, & Vasic, 2007; Vasic, et al., 2009). Across inhibition, shifting, and updating WM tasks, aberrant activity is reported in dorsolateral prefrontal cortex (DLPFC) and dorsal and rostral anterior cingulate cortex (ACC; inhibition: Engels et al., 2010; Herrington et al., 2010; Matthews, et al., 2009; Mitterschiffthaler et al., 2008; Wagner et al., 2006; shifting: Halari et al., 2009; Heinzel, et al., 2010; updating WM: Harvey et al., 2005; Matsuo et al., 2007; Rose, Simonotto, & Ebmeier, 2006). Other regions that have exhibited atypical activity include bilateral inferior frontal gyrus (IFG) and middle frontal gyrus on inhibition tasks (Engels et al., 2010; Kikuchi et al., 2012; Matthews, et al., 2009), parietal lobes on shifting tasks (Halari et al., 2009; Heinzel et al., 2010), and IFG and parietal lobes on updating WM tasks (Fitzgerald et al., 2008; Harvey et al., 2005; Vasic, et al.,

2009; Walsh et al., 2007; Walter et al., 2007). Importantly, these findings have been reported in the context of both normative and deficient behavioral performance, suggesting that even when individuals with depression are able to complete tasks (i.e., they are effective), they complete them in an atypical manner (i.e., they are inefficient).

Research that has investigated the association between depression and EF deficits among adults has primarily focused on its relationship with current depression. Because of this there has been an assumption in the literature that EF deficits are caused by active clinical depression. However, there is evidence that many of the EF deficits remain even upon remission and even after controlling for residual symptoms. Although there is some variation across studies, not only do some of these deficits not improve to the level of controls, they do not always improve within individuals (Trichard et al., 1995; Reppermund, Ising, Lucae, & Zihl, 2009). Notably, meta-analyses that have quantified the effect of remitted depression on inhibition, shifting, and updating WM report significant effects that are quite comparable to those of current depression (see Table 2, p. 61; Bora, Harrison, Yucel, & Pantelis, 2012; Rock et al., 2014). Specifically, in individuals with past depression there is a large effect for Stroop Interference RT (d = .74) and moderate effects for Intra-Extradimensional Set Shifts (d = .53), Trail Making Test Part B (d = .48), and Spatial Working Memory Task Errors (d = .53; Bora et al., 2012; Rock et al., 2014). As with current depression, past depressive symptoms have been associated with EF deficits in a non-clinical sample (Bredemeier et al., 2016).

One potential conclusion that researchers may make from available data is that active depression initially leads to EF deficits and EF deficits that remain following depression represent a "scar" of depression (for a discussion of scars in depression, see Wichers, Geshwind, Os, & Peeters, 2010). However, because these relationships are typically not assessed using

causal methods, possible alternatives must be explored. One plausible alternative is that EF deficits may not just contribute to the cognitive dysfunction found in depression, but to onset or maintenance of other symptoms of depression, including depressed mood and feelings of worthlessness. Although non-prospective, findings that disorders and injuries impacting EF are associated with higher rates of depression and depressive symptoms (e.g., attention deficit hyperactivity disorder (ADHD): Birchwood & Daley, 2012; Blackman, Ostrander, & Herman, 2005; frontal lobe lesions associated with traumatic brain injury: Fedoroff et al., 1992) may be taken as evidence that EF deficits may contribute to depression. Although it could be argued that depression may account for some of the ADHD symptoms, ADHD is considered a neurodevelopmental disorder that emerges in early childhood and is typically diagnosed before the onset of depression (which usually occurs in adulthood).

As Austin et al. (2001) suggest, EF deficits may not merely be a byproduct or epiphenomenon in depression, and some of the dysfunction in daily life reported by individuals with depression could be attributable to EF deficits rather than "depression" per se (Rappaport et al., 2005). Available prospective studies have revealed some support for EF predicting future depressive symptoms (Agoston & Rudolph, 2016; Rudolph, Monti, & Flynn, 2017; Letkiewicz et al., 2014). For example, self-reported EF (inhibition, shifting, and updating WM) prospectively predicted increases in depressive symptoms among young adults over approximately three months (Letkiewicz et al., 2014). In another study, observer-reported EF predicted adolescent girls' depressive symptoms over two years (Rudolph et al., 2017). Specifically, poorer shifting as reported by teachers predicted greater symptoms of depression. Another study found that poorer updating WM predicted more negative mood states over the course of one week among

adolescents, although they did not examine whether this was specific to depression (Papadakis, Fuller, Brewer, Silton & Santiago, 2017).

There are several pathways through which EF deficits may contribute to future depression. If individuals have difficulty inhibiting automatic or prepotent responses, shifting flexibly between tasks or goals, or updating (i.e., revising) information that is actively being held in WM, they may not be able to perform adequately at work or school, which could be distressing. Suggestive of this possibility, difficulties with sustaining and regulating attention (important aspects of EF) mediate the relationship between ADHD and depressive symptoms (Blackman et al., 2005). Thus, distress and depressed mood may emerge as a result of academic difficulties and/or social difficulties that arise from EF deficits. EF impairments may also create difficulties disengaging from emotional information. For example, in adolescents, self-reported set-shifting deficits predicted higher levels of rumination, and higher levels of rumination predicted increases in depressive symptoms across two weeks (Dickson, Ciesla, & Zelic, 2016). Among adults, rumination was found to mediate the relationship between another EF processes, self-reported WM, and future depressive symptoms across three months (Letkiewicz, 2013, unpublished master's thesis). Highlighting the role of both stress and rumination in the relationship between EF and depression, poorer EF was found to prospectively predicted greater self-induced stress among children and adolescents, which predicted greater future depressive symptoms (Snyder & Hankin, 2016). Furthermore, greater self-induced stress predicted more rumination, which in turn predicted future depressive symptoms (Snyder & Hankin, 2016).

Overall, while there is evidence available that indicates that EF deficits predict future depression and future depressive symptoms, prior prospective research has typically assessed only one or two EF processes, used one or two tasks to measure EF processes, or used self-

reported EF only. Although some studies that have examined the role of EF in depression among children and adolescents have used multiple measures of EF, results cannot be assumed to generalize to young adults and adults. It is possible that maturation of the frontal lobes and/or the development of compensatory strategies may alter associations between EF processes and depression. Indeed, a recent study found that among children and adolescents, the best fitting EF model was a single-factor model (Karr et al., 2018), whereas adults exhibited greater evidence of EF differentiation and specialization among EF processes. Given that the burden of depression has continued to increase despite scientific successes, there is still room for improvement in our understanding of the causes of depression. Because there are strong relationships between EF in both current and remitted depression, this is a prime avenue exploration that may yield important information for prevention or treatment efforts.

CHAPTER 2: STUDY 1

Introduction

The primary goal of the first study was to build on previous work by examining whether EF prospectively predicts future depressive symptoms over 3 months using both a self-report measure and a task-based assessment of EF. The inclusion of both assessments provides a more comprehensive understanding of how EF is related to depressive symptoms (Barkley & Murphy, 2011; Barkley & Murphy, 2010; Knouse, Barkley, & Murphy, 2013; Toplak, West, & Stanovich, 2013). Self-reported EF measures are designed to index performance in daily life, thus having ecological validity, and have been found to be sensitive to subtle EF deficits that are not evident on task-based assessments (Rabin et al., 2006). However, it has been argued that self-reported EF may not accurately depict cognitive function and thus a well-validated task-based assessment of EF, the n-back task, was also utilized.

In Study 1, depressive symptoms were measured instead of depression as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM), which uses a categorical approach. Reasons for the assessment of dimensional symptoms include evidence that suggests that depression is well-captured by a dimensional approach (Bredemeier et al., 2010; Hankin, Fraley, Lahey, & Waldman, 2005; Lewinsohn, Solomon, Seeley, & Zeiss, 2000; Ruscio & Ruscio, 2000) and evidence that subthreshold symptoms not captured by a DSM-based diagnosis still impact functioning and thus are clinically relevant (Lewinsohn et al., 2000). Indeed, EF impairment and altered neural functioning in brain regions known to implement EF have been associated with symptoms of depression as measured dimensionally in non-clinical samples (Engels et al., 2010; Herrington et al., 2010; Letkiewicz et al., 2014; Sass et al., 2014; Silton et al., 2011).

A notable limitation of past work is that the potential impact of co-occurring anxiety has not always been taken into account. Although Snyder (2013) reported that taking into account co-occurring psychopathology, including anxiety, did not significantly alter any findings, individuals can have elevated levels of anxiety symptoms that may impair functioning without meeting criteria for an anxiety disorder. Taking dimensions of anxiety into account is critical because depression and anxiety often co-occur, and anxiety has been associated with EF deficits as well as aberrant neural activity during tasks that assess EF, which could account for some of the results (Balderston et al., 2017; for review, see Castenada et al., 2008; Engels et al., 2007; Engels et al., 2010; Herrington et al., 2010; Letkiewicz et al., 2014; Silton et al., 2011; Vytal et al., 2013). Additionally, it is important to account for co-occurring anxiety because anxiety may alter or obscure the associations between EF deficits and depression. For example, a significant association between depression symptoms and IFG activity during the Stroop task only emerged after controlling for co-occurring anxiety (Engels et al., 2010). Thus, taking anxiety into account will help to clarify relationships between EF and depression by determining if anxiety accounts for some of the EF impairment associated with depression, and/or revealing relationships that may have previously been obscured.

For Study 1, an undergraduate sample was selected to examine whether EF confers risk for future depressive symptoms because these individuals are an age that is below the median age of onset of depression, which is 32 years old (Kessler et al., 2005). Three months was selected for the follow-up period because a similar time frame previously revealed prospective associations between EF and psychopathology symptoms in previous studies (Bredemeier & Berenbaum, 2013; Letkiewicz et al., 2014). Based on prior work it is hypothesized that

depressive symptoms will be significantly associated with deficits on both self-reported and task-based measures of EF at T1 and T2, even after accounting for co-occurring symptoms of anxiety.

Method

Participants.

Participants were recruited through introductory psychology courses. During an initial session, individuals provided informed written consent, completed two computerized tasks and online questionnaires, were compensated with course credit, and were given the opportunity to provide their consent to future contact for a planned follow-up study. Participants were informed that providing consent to future contact was voluntary and did not contract them into any future studies. Approximately three months later, individuals who provided consent to future contact and who were interested in proceeding with the follow-up study provided informed online consent, completed online questionnaires, and were financially compensated (see Figure 1 for an overview of the Study 1, p. 74). All portions of the present research study were approved by the University of Illinois at Urbana-Champaign Institutional Review Board and all procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (University of Illinois at Urbana-Champaign) and with the Helsinki Declaration of 1975, as revised in 2000.

Apriori power analyses indicated that associations that are small (.15), small to medium (.20), or medium (.30) in size could be detected 80% of the time with a sample size of N = 346, N = 194, and N = 85, respectively (R package: pwr, Champely, 2012; Champely et al., 2017). Power analyses also revealed that after accounting for variance with a set of predictors that have a medium to large effect size (R^2 = .25, selected based on previous research; e.g., Letkiewicz et al., 2014), a small effect (R^2 = .02) could be detected 80% of the time with a sample of N = 291

and a small to medium sized effect (R^2 = .06) could be detected with a sample of N = 95. Because some of the prior research found small to medium sized associations between depressive symptoms and task-based measures of EF (e.g., Bredemeier et al., 2016), Study 1 sought to recruit a large sample of participants to be able to detect even small associations.

Questionnaires.

At the initial session (T1) and at follow-up (T2), participants completed measures to assess current depressive and anxiety symptoms. Depressive symptoms were measured with the 8-item Anhedonic Depression subscale of the Mood and Anxiety Symptom Questionnaire (MASQ-AD; Watson et al., 1995a; Watson et al., 1995b). In addition, two different dimensions of anxiety were assessed (Nitschke, et al., 2001; Engels et al., 2007; Sass et al., 2010): anxious arousal, which is associated with physiological arousal and panic symptoms and was measured with the 17-item Anxious Arousal subscale of the MASQ (MASQ-AA), and anxious apprehension, which is associated with worry and somatic tension and was measured with the 16-item Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990; Molina & Borkovec, 1994). Other questionnaires were included at T1 and T2, but these are not included in present analyses.

Self-reported Executive Function.

At times 1 and 2 participants completed 22 items plus two validity questions from the 75-item Behavior Rating Inventory of Executive Function (BRIEF) Adult Version (Roth, Isquith, & Giaoia, 2005). These items were selected for inclusion to assess three components of EF: Inhibit (8 items; e.g., “I have problems waiting my turn”), Shift (6 items; e.g., “I have trouble changing from one activity to another”), and Working Memory (WM: 8 items; e.g., “I forget what I am doing in the middle of things”). The BRIEF is a self-report measure intended to assess EF over

the past 6 months in an ecologically sensitive manner (e.g., Rabin et al., 2006). Higher Inhibit, Shift, and WM scores represent worse EF.

Updating Working Memory Tasks.

At T1 all participants completed a computer-based visual-spatial and verbal 2-back version of an n-back task that was previously included in a study by Bredemeier and Berenbaum (2013). Task order was counterbalanced across participants. The 2-back tasks consisted of 5 blocks of 20 trials, with the first block utilized as a practice block. During the visual-spatial version of the task, participants indicated whether the current letter that was being presented was in the same location on the computer screen as the letter 2 trials back by pressing either "s" (same) or "d" (different) on the keyboard. During the verbal version of the task, participants indicated whether the current letter that was being presented was the same as the letter 2 trials back by pressing either "s" or "d" on the keyboard. Both uppercase and lowercase letters were included to counter the use of visual memory alone in the verbal condition, but individuals were informed that letter case was irrelevant (in other words, an uppercase "A" was equivalent to a lowercase "a").

Each n-back task included five blocks with 20 trials per block. The first block was treated as a practice block and therefore was excluded from analyses. During a given trial locations/letters were presented on the screen for 500 ms, with a 2000 ms intertrial interval. Since the first two trials of each block do not correspond to two prior trials, the first two trials in each block were excluded. The dependent variable for each n-back task was accuracy (out of 72 possible responses; 4 blocks, 18 response trials per block). Because only two possible responses are available on each trial (same or different), guessing was controlled for by only including individuals that had greater than 50% accuracy on each version of the n-back task.

Addressing Missing Data.

Participant dropout is important to consider in longitudinal studies, since the missing data can lead to biased population parameter estimates (i.e., estimated parameters differ from the true population parameters) and can decrease statistical power (Graham, 2009; Jelicic et al., 2009). Although taking steps to prevent attrition is the best approach (e.g., by increasing the likelihood that participants complete a study in full), it is not always possible to prevent participant dropout. There are several statistical approaches that help to decrease the likelihood that parameter estimates will be biased and to retain statistical power when dropout occurs. A few approaches that are commonly used to handle missing data include listwise deletion, pairwise deletion, carrying forward previous data values, and replacing missing data with means. However, it is recommended that these approaches not be used when more than 5% of the data is missing, as this can lead to substantial bias and/or loss of power (Dong & Peng, 2013; Graham, 2009; Jelicic et al., 2009; Newman, 2003). When greater than 5% of the data is missing it is recommended that approaches be used to estimate the missing data, such as multiple imputation (MI) and full-information maximum likelihood (FIML). MI estimates missing data through randomly drawing parameter estimates from a Bayesian posterior distribution of regression estimates that are based on available observed data, whereas FIML uses likelihood functions to estimate data (first estimating a parameter where cases are complete and then where cases are not complete and maximizing these together; Newman, 2003). Both MI and FIML yield less biased parameter estimates than listwise and pairwise deletion (Jelicic et al., 2009). Furthermore, both result in acceptable parameter estimation even when 50-75% of the data is missing (Jelicic et al., 2009). While neither approach is generally superior (Graham, 2009), one potential advantage of MI over FIML is that it may be more robust for data that exhibits skewness (Newman, 2003).

As is the case with FIML, MI should only be used when the data is either missing completely at random (MCAR) or missing at random (MAR). When data are MCAR it is equally likely to be missing at all time points for all variables or items (i.e., it is not missing in a systematic manner). Under this condition, estimates of the missing data are unlikely to be biased (Newman, 2003). When data are MAR, the data is not missing in a manner that is systematically related to a study's questions of interest. Whereas MCAR and MAR are acceptable conditions for MI, MI and all other estimation techniques perform poorly when data are not missing at random (NMAR; Newman, 2003). Under NMAR conditions, missing data are systematically missing in a manner that is related to a study's questions of interest. It was anticipated that any data missing from Study 1 would not be missing in a nonrandom manner (i.e., are not NMAR). A check for systematic differences among individuals who did and did not complete the study was implemented prior to MI.

Results

Sample demographics.

Four hundred and fifty-four individuals participated at T1 and 164 individuals participated at T2 (36% of those initially recruited). The average length of time between the initial and follow-up session was 98.75 days (SD = 5.27). This sample size was substantially larger than in previous studies that found significant associations between EF and dimensional symptoms of psychopathology longitudinally (e.g., Bredemeier & Berenbaum, 2013; Letkiewicz et al., 2014; N = 38 and N = 52, respectively). At T1, 11 verbal n-back and 5 spatial n-back accuracy scores were missing (2.4% and 1.1%, respectively). At T2, psychopathology symptom scores were missing from the study non-completers (N = 290; 64% of each symptom measure). No other T2 data were missing.

Prior to MI, potential differences between study completers and non-completers on T1 variables were examined to check whether data were systematically missing on the basis of study completion status. No differences were evident on any of the T1 variables (see Table 3, p. 62). MI was implemented using available data from all participants (specifically, study completion status, age, gender, self-reported inhibition, shifting, working memory, verbal n-back accuracy, spatial n-back accuracy, T1 anhedonic depression, T1 anxious apprehension, T1 anxious arousal, and available T2 anhedonic depression scores) to estimate the missing data. Missing variables estimates were imputed 10 times and the results of these imputations were combined into a final data set (R package: mice; van Buuren & Groothuis-Oudshoorn, 2011). No differences were found between imputed and non-imputed T2 anhedonic depression scores, $t(452) = .42$, $p = .674$.

Following MI, individuals were excluded if they had an n-back accuracy below chance performance (< 50%) on either the verbal or spatial version of the task. For remaining participants, verbal and spatial accuracy scores were averaged together to create an updating WM score. The final sample included 355 participants who were, on average, 18.9 years old (SD = 1.1). Two hundred and thirty-five participants identified their gender as female (66%; male = 34%) and most participants identified their race as White (67.9%), followed by Asian (13%), Black or African American (10%), more than one race (5.7%), unknown or preferred not to answer (3.2%) and American Indian or Alaskan Native (0.3%). See Table 4 (p. 63) for descriptive statistics.

Time 1 Self-reported EF and Current Depressive Symptoms.

Zero-order correlations revealed significant positive associations between self-reported EF on the BRIEF subscales and symptoms of depression at T1 (note: higher scores on the BRIEF represent worse functioning; see Table 5, p. 64). Next, three separate linear regressions (one each

for Inhibit, Shift, and WM) were used to examine whether the associations between self-reported EF and depressive symptoms remained after controlling for co-occurring anxiety. T1 anxious apprehension and anxious arousal were included as predictors of anhedonic depression in Step 1 and BRIEF subscales were entered in Step 2. Self-reported EF continued to predict a unique portion of variance in depressive symptoms after controlling for T1 anxiety, Inhibit: total R^2 = .35, ΔR^2 = .04, *B* = .22, *F-change* (1, 351) = 23.61, $p < .001$, Shift: total R^2 = .34, ΔR^2 = .04, *B* = .23, *F-change* (1, 351) = 19.61, $p < .001$, and WM: total R^2 = .33, ΔR^2 = .02, *B* = .17, *F-change* (1, 351) = 12.57, $p < .001$.

Time 1 Task-Based EF and Current Depressive Symptoms.

Correlations revealed a significant association between n-back accuracy and anhedonic current depressive symptoms, $r(353) = -.18$, $p = .001$. A hierarchical linear approach was used to examine whether there was a significant association between the task-based measure of updating WM and symptoms of anhedonic depression after T1 symptoms of anxiety were accounted for. Anxious arousal and anxious apprehension were entered into Step 1 and n-back accuracy was entered into Step 2. N-back accuracy predicted a significant portion of variance in depressive symptoms after accounting for symptoms of anxiety, total R^2 = .32, ΔR^2 = .02, *B* =-.12, *F-change* (1, 351) = 7.70, $p = .006$.

Time 1 Self-reported EF and Future Depressive Symptoms.

All three subscales of the BRIEF at T1 were significantly associated with depressive symptoms at T2 (see Table 5, p. 64). Three separate hierarchical regressions (one each for Inhibit, Shift, and WM) were used to examine whether associations between the BRIEF subscales and depressive symptoms at T2 remained after controlling for the potential influence of T1 psychopathology symptoms. T1 depressive and anxiety symptoms were entered into Step 1

and BRIEF subscales were entered into step 2. Self-reported shifting continued to predict a unique portion of variance in T2 depressive symptoms, total R^2 = .33, ΔR^2 = .01, *B* = .11, *F-change* (1, 350) = 4.51, *p* = .034, whereas inhibition and WM did not (Inhibit: total R^2 = .33, ΔR^2 = .00, *B* = -.01, *F-change* (1, 350) = .02, *p* = .886; WM: total R^2 = .33, ΔR^2 = .007, *B* = .09, *F-change* (1, 350) = 3.45, *p* = .064).

Time 1 Task-Based EF and Future Depressive Symptoms.

N-back task accuracy at T1 was significantly associated with depressive symptoms at T2, *r*(353) = -.16, *p* = .003. To examine whether an association between updating WM and symptoms of anhedonic depression at T2 remained after T1 symptoms of anxiety were accounted for, a hierarchical regression was used. N-back accuracy did not predict a significant portion of variance in T2 depressive symptoms after taking into account baseline depressive and anxiety symptoms, total R^2 = .32, ΔR^2 = .001, *B* = -.06, *F-change* (1, 350) = 2.08, *p* = .150.

Self-Reported and Task-Based EF.

Performance on each of the BRIEF subscales was significantly correlated with n-back accuracy, Inhibit: *r*(353) = -.16, *p* = .002, Shift: *r*(353) = -.15, *p* = .005, and WM: *r*(353) = -.18, *p* = .001.

Discussion

Results of Study 1 replicate and extend previous work that shows a consistent, medium-to-large sized relationship between categorically-based, DSM-diagnosed depression and EF impairment among adults by revealing that both poorer self-reported and task-based EF deficits predict higher clinical symptoms of depression. With regard to current depressive symptoms, associations between self-reported EF and depressive symptoms were medium to large in size, whereas the association between the task-based measure of updating WM and depressive

symptoms was small to medium. After accounting for co-occurring symptoms of anxiety, current depressive symptoms continued to predict both self-reported and the task-based measure of EF, indicating that neither worry nor heightened anxious arousal fully account for the relationship between EF deficits and current depressive symptoms. Similar to current depressive symptoms, EF predicted depressive symptoms at T2. Contrary to the hypothesis that poorer self-reported and task-based EF broadly would continue to predict future depressive symptoms after controlling for initial symptoms of depression and anxiety, only self-reported shifting predicted future depressive symptoms after accounting for baseline symptoms.

The finding that current depressive symptoms are related to both self-reported and task-based updating WM deficits is in line with meta-analyses that have revealed relationships between broad EF deficits and current DSM-diagnosed depression (e.g., Snyder, 2013). This is also consistent with a study which found that broad, task-based EF predicts current depressive symptoms among adolescents unselected for psychopathology (Han et al., 2016). In contrast, more specific deficits appear to contribute to future depressive symptoms above baseline symptoms of depression and anxiety. There is support for the latter in Letkiewicz et al. (2014), which found that only one facet of EF, self-reported WM, uniquely predicted future depressive symptoms across 3 months. In contrast to Letkiewicz et al. (2014), specificity for WM was not supported in the present study by either the self-report or task-based measures, as only self-reported shifting emerged as a significant predictor. In support of a potential role of shifting deficits in future depression, Rudolph et al. (2017) found that poorer self-reported shifting predicted future depressive symptoms among middle school females, although other facets of EF were not reported. Similarly, Dickson et al. (2016) found that self-reported shifting deficits predicted higher levels of future depressive symptoms within a non-clinical sample of

adolescents. Furthermore, they found that this relationship was specific to shifting, as self-reported inhibition did not predict future depression. In contrast, Han et al. (2016) found that neither broad nor specific EF factors, including shifting, predicted future depressive symptoms among adolescents. Overall, substantial variation in results across studies makes it difficult to draw strong conclusions about the role of EF in future depression. It will be important to identify potential sources of variation to better interpret results.

A notable limitation of Study 1 concerns the use of only one task-based EF measure. Although current depressive symptoms were related to updating WM, it cannot be assumed that this result would extend to other EF processes. Thus, it is unclear, at least on the basis of standardized EF measures, that current depressive symptoms are associated with broad deficits in EF. Additionally, lack of associations between updating WM and future depressive symptom residuals does not preclude the possibility that future depression is associated with other task-based EF deficits, and thus should be explored further.

Another limitation of Study 1 concerns the use of the 2-back version of the n-back task to assess updating WM. Despite associations between 2-back performance and depressive and anxious apprehension symptoms, associations were small (r = -.18 and -.12, respectively). One possibility is that this particular task is not sensitive enough to detect relationships among young adults. Although effects of depression on WM performance have been detected among adolescents and young adults, this appears to be task dependent (Baune, Fuhr, Air, & Hering, 2014). For example, Baune et al. (2014) found that depression was associated with poorer performance on Spatial Span and Spatial WM tasks, this was not the case for the 2- or 3-back versions of the n-back task. Although the 3-back task is more difficult, even that version of the task may not be an adequate measure of updating WM for young adults, as it is only slightly

more difficult than the 2-back task. Furthermore, the 3-back has been found to have insufficient reliability, indicating that it is not an ideal measure for assessing intraindividual associations (Jaeggi, Buschkuehl, Perrig, & Meier, 2010).

Overall, results indicate that EF deficits are related to current and future depressive symptoms, with current depressive symptoms associated with broad EF deficits and future depressive symptoms with more specific EF deficits. Although EF deficits played a relatively modest role in current and future depressive symptoms in Study 1, it is notable that relationships emerged even among individuals who were unselected for clinical symptoms or psychopathology risk. Furthermore, not only did relationships emerge, the pattern of associations between current depressive symptoms and impairment in multiple EF processes seen in clinical samples was replicated, indicating that a dimensional relationship between depressive symptoms and EF impairment extends beyond clinical diagnosis. Given that the relationships were small in size, however, it will be critical in future work to assess whether these associations emerge to a larger degree among individuals at risk for depression.

CHAPTER 3: STUDY 2

Introduction

The second study sought to build on Study 1 and other previous work by examining the prospective relationship between EF and depressive symptoms over three years using multiple measures of EF. As with Study 1, participants were selected via introductory psychology courses, a dimensional approach to depression was utilized, and co-occurring anxiety was assessed. In contrast to Study 1, participants were recruited on the basis of high, average, and low risk for depression. At T1, individuals completed a state-of-the art neuropsychological assessment of EF, a questionnaire session, and an fMRI session (note: EEG was also collected but is not included in the present study). During the fMRI session participants completed a locally developed, modified version of the Monetary Incentive Delay task that includes components of the Emotional Stroop task. After three years a follow-up assessment was conducted with a subset of individuals from T1. During the follow-up assessment participants completed a questionnaire session, a subset of neuropsychological assessments that were completed at T1, and a diagnostic interview. Three years was selected as the time period between the initial assessment and follow-up assessment because although the median age of onset of depression is 32, the typical age range of onset is between 25 and 44 years old (Kessler et al., 2005). Thus, this follow up period would allow for an examination of change in depressive symptoms over a time that individuals would increasingly be likely to develop depression but still be outside of the typical age of onset to be able to focus on risk. Another advantage of using a college sample to examine risk is that college is a natural stressor which could prompt depressive symptoms to emerge for those at risk (Ross, Niebling, & Heckert, 1999).

In Study 2, neuropsychological assessments and fMRI were included to assess both cognitive effectiveness and efficiency. The neuropsychological assessments employed were well-standardized and designed to measure targeted aspects of EF (e.g., inhibition). Furthermore, there is a rich foundation of neuropsychological assessment data to build on with regard to cross-sectional research, and building on this foundation using similar measures will help make findings more interpretable. However, deficits on neuropsychological measures may not always be evident (for example, when assessing risk before a disorder has occurred) and thus other methods provide an important complement. fMRI is particularly useful with this regard because functional differences may not yet be evident on neuropsychological assessments (e.g., effective but inefficient processing), but could have implications for future functioning. Thus, what may not be "visible" yet through neuropsychological assessment may be detected with neuroimaging. If deficits are evident on neuropsychological assessments, fMRI can also be useful in indicating what aspects of brain functioning may be contributing to aberrant performance (e.g., difficulty with imposing a task set or with monitoring conflict).

Study 2 sought to examine neural activity associated with inhibitory function during an fMRI task. Inhibitory function was selected to be examined using fMRI because prior work has revealed consistent, strong associations between inhibition deficits and current and remitted depression (Snyder, 2013; Bora et al., 2012); therefore, it is a particularly important aspect of EF to examine prospectively. As stated above, studies that have examined which brain regions are activated during tasks that require inhibition have found significant activations for dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), and inferior frontal gyri (IFG; Gruber, Rogowska, Holcomb, Soraci, & Yurgelun-Todd, 2000; Langenecker, Nielson, & Rao, 2004; for review, see Niendam et al., 2012). Left DLPFC is purported to play an important role

in imposing an attentional task set and implementing cognitive control (Banich et al., 2000; MacDonald III, Cohen, Stenger, & Carter, 2000). Broadly, ACC is involved in performance and conflict monitoring (MacDonald III et al., 2000), and specific regions of ACC are involved in different aspects of conflict resolution. Whereas dorsal ACC (dACC) exhibits increased activity in the face of competing information and is purported to facilitate response selection and adjustment following errors, rostral ACC (rACC) exhibits increased activity when individuals are confronted with emotionally salient, distracting information and is suggested to regulate or control distraction by this information (e.g., by decreasing activity in the amygdala; Mohanty et al., 2007). Both left and right IFG are implicated in response inhibition, although right IFG is more strongly and consistently associated with inhibitory motor control than left IFG (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Swick, Ashley, & Turken, 2008; for review, see Verbruggen & Logan, 2008).

The present study utilized an fMRI task that incorporated an assessment of inhibition based on the Emotional Stroop Task. The Emotional Stroop Task is a modified version of the traditional Stroop Task that includes emotional words instead of color names. Although there is not a direct conflict between word meaning and ink color in the Emotional Stroop Task, conflict arises because emotional words capture attention and must be ignored to quickly identify the ink color of words. Previous cross-sectional studies have revealed significant associations between depression and aberrant neural activity during the Emotional Stroop Task in brain regions associated with inhibitory control (Mitterschiffthaler et al., 2008). For example, Mitterschiffthaler et al. (2008) found that depressed patients exhibit greater rACC activity and right precuneus activity for negative versus neutral words (a negative affect contrast) during the Emotional Stroop task. Furthermore, in the depressed group, greater rACC activity was

associated with increased RT for negative words, suggesting that depressed individuals have particular difficulty inhibiting negative information.

Atypical brain activity during the Emotional Stroop has also emerged for individuals who were not recruited on the basis of DSM-diagnosed depression (Engels et al., 2010; Herrington et al., 2010). For example, depressive symptoms were associated with greater dACC and rACC activity when contrasting negative to neutral words in undergraduates (Engels et al., 2010). Furthermore, greater activity in these regions was associated with greater RT interference (RT for negative words minus RT for neutral words; Engels et al., 2010). Notably, depressive symptoms uniquely predicted activity in dACC and rACC, as this activity was not accounted for by co-occurring anxiety symptoms. Activity in other regions was also associated with elevated levels of depression (e.g., elevated activity in right DLPFC and reduced activity in right IFG), but this activity depended on co-occurring anxiety. Undergraduates placed into a "depression" group based on elevated depressive symptoms and low anxiety symptoms were also found to exhibit atypical neural activity during an Emotional Stroop Task (Herrington et al., 2010). Specifically, depressed participants exhibited greater right-lateralized activity than controls for negative versus neutral words in an area of the frontal lobe which included DLPFC and IFG. This finding was primarily driven by more activity for negative words in the right versus left hemisphere. A valence contrast (positive minus negative words) also revealed atypical activity, with controls exhibiting marginally more left-lateralized DLPFC activity than depressed participants.

Based on previous findings, it was hypothesized that depressive symptoms will be significantly associated with EF deficits captured via standardized neuropsychological assessment performance and by self-report at time 1 (T1) and time 2 (T2), even after accounting

for co-occurring symptoms of anxiety. Furthermore, it was anticipated that these EF deficits would predict future depressive symptoms above baseline depressive and anxiety symptoms, and past depression. Specifically, it was predicted that poorer EF would be associated with increases in depressive symptoms over three years.

It was also hypothesized that aberrant neural activity in multiple brain regions during the emotional inhibition portion of the fMRI task at T1 would predict current and future depressive symptoms. First, it was hypothesized that for the negative affect contrast, increased dACC and rACC activity at T1 would predict depressive symptoms at T1 and T2 (Engels et al., 2010; Herrington et al., 2010; Mitterschiffthaler et al., 2008). It was also predicted that reaction time (RT) interference at T1 would be associated with increased activity in these regions at T1.

Additionally, it was hypothesized that depressive symptoms at T1 and T2 would be predicted by elevated activity in right DLPFC activity. However, given the finding that activity in right DLPFC depends on co-occurring anxiety (e.g., Engels et al., 2010), it was anticipated that these results may not hold after accounting for co-occurring anxiety. Elevated IFG activity was expected to predict depressive symptoms at T1 and T2, but that this relationship may only emerge after controlling for co-occurring anxiety symptoms.

With regard to the positive affect contrast, prior research indicates that positive information does not readily capture attention and is processed to a lesser degree by individuals with depression and those who are at risk for depression (Bermpohl et al., 2009; Canli et al., 2004; Epstein et al., 2006; Fu et al., 2007; Joormann & Gotlib, 2006; Mitterschiffthaler et al., 2008; Surguladze et al., 2004). Because less attentional capture would lead to reduced need for inhibitory control, it was hypothesized that lower activity for positive relative to neutral words would be associated with depressive symptoms at T1 or T2.

With regard to the arousal contrast, effects have often depended on co-occurring levels of anxiety (Engels et al., 2010; Sass et al., 2014). Because depression is generally associated with decreased attention to positive (yet arousing) stimuli compared to controls, it was anticipated that any significant effects for depressive symptoms would not hold after accounting for anxiety. With regard to valence, it was anticipated that depressive symptoms at T1 and T2 would be predicted by lower activity in response to positive words coupled with greater activity in response to negative words in right DLPFC. Furthermore, it was anticipated that this pattern of activity would not be accounted for by co-occurring anxiety. Across contrasts, associations between significant neural activity, RT interference, and neuropsychological assessments of inhibition (standardized and self-report) were explored.

Finally, because the tendency for emotional words to capture attention depends to some extent on individual differences in sensitivity to certain types of emotion, the need to activate inhibitory processes will likely very across individuals. In other words, inhibitory processes may not be strongly activated in individuals whose attention is not strongly captured by negative words. Previous work by Hur et al. (2015) found that individuals only exhibited aberrant neural activity and impaired performance on an EF task during negative mood states when they had high levels of trait negative affect. Therefore, the moderating effect of trait negative affect on the aforementioned brain activity was explored.

Method

Participants.

Participants were initially recruited via introductory psychology courses to complete a questionnaire screening session, for which they received course credit. Individuals who completed the initial questionnaire session were invited to participate in the T1 study session if

they met criteria on the basis of trait affect using the Positive and Negative Affective Schedule (PANAS). To capture a range of low, average, and high risk for psychopathology, individuals were recruited to have high positive affect (PA) coupled with low negative affect (NA; scores ≥ 80^{th} and < 50^{th} percentile, respectively), low PA coupled with low NA (scores < 50^{th} percentile), and high NA coupled with low PA (scores ≥ 80^{th} percentile and < 50^{th} percentile, respectively). Individuals who met these criteria and provided written informed consent to participate were screened for a history of serious brain injury, abnormal hearing or vision, claustrophobia, left-handedness, metal in their body, pregnancy, and nonnative English-speaking. In total, 103 undergraduates met criteria for inclusion and participated at T1 with approximately an equivalent number of individuals in the high PA/low NA group (N = 35, 34%), low PA/high NA group (N = 32, 31%), the low PA/low NA group (N = 36, 35%). Participants who completed T1 of the study and who consented to future contact were invited to participate in a T2 follow-up study 3 years later (see Figure 2 for an overview of the study, p. 74). Forty-eight individuals who completed the T1 study session also participated at T2 (47%). Initial PA/NA groupings were not utilized in the present analyses.

All portions of the present research were approved by the University of Illinois at Urbana-Champaign Institutional Review Board. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (University of Illinois at Urbana-Champaign) and with the Helsinki Declaration of 1975, as revised in 2000. At T1 all participants provided informed written consent, completed questionnaires and neuropsychological assessments, and were financially compensated. At the end of the T1 study, individuals were provided an opportunity to consent to future contact for a future follow-up study. Participants were informed that providing consent to future contact was voluntary and did

not contract them into future studies. Approximately three years later (T2), individuals who provided consent to future contact and who were interested in proceeding with the follow-up study provided informed written consent, completed questionnaires, neuropsychological assessments, and a structured clinical interview, and were financially compensated.

Time 1 Measures.

Questionnaires.

Participants completed measures of current depressive and anxiety symptoms. Depressive symptoms were measured with the 8-item Anhedonic Depression subscale of the Mood and Anxiety Symptom Questionnaire (MASQ-AD; Watson et al., 1995a; Watson et al., 1995b). In addition, two different dimensions of anxiety were assessed (Nitschke, et al., 2001; Engels et al., 2007; Sass et al., 2010): anxious arousal, which is associated with physiological arousal and panic symptoms and was measured with the 17-item Anxious Arousal subscale of the MASQ (MASQ-AA), and anxious apprehension, which is associated with worry and somatic tension and was measured with the 16-item Penn State Worry Questionnaire (PSWQ; Meyer et al., 1990; Molina & Borkovec, 1994).

Structured Clinical Interview.

Participants were assessed for Axis I psychopathology using the Structured Clinical Interview for DSM-IV Disorders (SCID-NP; First, Spitzer, Gibbon, & Williams, 2002). Clinical interviews were conducted by advanced doctoral students in clinical psychology. Individuals were given a coding of 1 in the present study if they currently met diagnostic criteria for a disorder and 0 if they did not meet diagnostic criteria.

Self-Reported Executive Function.

Participants completed the 75-item Behavior Rating Inventory of Executive Function (BRIEF) - Adult Version (Roth et al., 2005). The BRIEF is a self-report measure intended to assess EF over the past 6 months in an ecologically sensitive manner. For the present study, the Inhibit (8 items; e.g., "I have problems waiting my turn"), Shift (6 items; e.g., "I have trouble changing from one activity to another"), and Working Memory (WM: 8 items; e.g., "I forget what I am doing in the middle of things") subscales were used to assess three EF components. Higher Inhibit, Shift, and WM scores represent poorer EF.

Executive Function Tasks.

Participants were given a lengthy set of laboratory measures of EF. The laboratory measures were selected to be state of the art, sensitive assessments of inhibition, shifting, and updating WM based on consultations with collaborators at the University of Colorado Boulder, Department of Psychology and Neuroscience and a review of relevant literature. The following tasks were selected to assess inhibition: the Delis-Kaplan Executive Function System (D-KEFS) Color-Word Interference Test (Delis, Kaplan, & Kramer, 2001) and Stop Signal Task (van den Wildenberg, 2006); shifting: the D-KEFS Trail Making Test (Delis, et al., 2001), D-KEFS Verbal Fluency Test (Delis, et al., 2001), and Plus-Minus Task (Jersild, 1927; Spector & Biederman, 1976); updating WM: the Keep Track task (adapted from Yntema, 1963; Miyake et al., 2000), Letter Memory task (adapted from Morris & Jones, 1990; Miyake et al., 2000), and a locally developed spatial updating task (Warren, Towers, Miller, & Heller, unpublished manuscript).

Dependent measures selected for this study were based on a review of the literature and prior work by the Heller-Miller Lab. Task details and dependent measures from each task are

described below. An ideal data analytic approach would be to determine the data's underlying factor structure (e.g., one factor versus three factors) and extract latent variables, which would help to address the task impurity problem (an issue which arises because most tasks require multiple aspects of EF to perform; Miyake et al., 2000; Snyder, Miyake, & Hankin, 2015). Because the sample is too small to utilize exploratory factor analysis, alternative strategies will be used. In addition to using individual task measures, a z-score composite will be created for each EF component that includes the dependent measures that are purported to tap into the same EF processes (e.g., inhibition; Snyder et al., 2015). Although error variance unrelated to EF processes is not partialed out using this approach, thereby providing less precision than latent factor extraction, composite measures are more reliable than single factor scores.

An alternative approach that will be used in Study 2 is the application of standardized factor weights from a single-factor EF model that was recently derived using overlapping neuropsychological assessment data (Madian et al., in press; total N = 125, overlap N = 103). A major challenge with applying factor weights from prior studies is that it is not always clear which factor weights should be used, as there is significant variation between studies regarding identified factor structure and factor weighting (Karr et al., 2018). Applying factor weights from a model derived with overlapping data will help to support the meaning and interpretability of results. Prior to applying the factor weights, model fit was examined with a confirmatory factor analysis (R package: llavan; Rosseel, 2012). The following standardized item loadings from Madian et al. (in press) were applied, Stroop: 0.772, Stop Signal: 0.258, Tower of London: 0.279, Plus-Minus: 0.487, Trails: 0.579, Verbal Fluency: 0.437, Spatial Updating: 0.319, Letter Memory: 0.494, and Keep Track: 0.613.

Inhibition.

D-KEFS Color-Word Interference Test. This task assesses participants' inhibition of prepotent responses. There are four conditions in this task, the third of which is a measure of inhibition. During the inhibition condition, participants are instructed to name the ink color of 50 consecutive words that are all printed in an ink color that is incongruent with the color name (e.g., the word "red" is printed in green ink). Participants are instructed to correctly identify the ink color of the words as quickly as they can "without making mistakes," which requires inhibiting the more automatic tendency to read the words. The dependent measure from this task is time to complete the inhibition condition. This outcome measure was multiplied by -1 for reverse-scoring, such that more negative numbers represent worse inhibitory ability.

Stop-Signal: This task assesses participants' inhibition of automatic responses. During this computer-based task participants indicate the direction that successively presented green arrows are pointing (either left or right) using the left and right keyboard keys. Participants are told that the arrow will change from green to red during some of the trials and that they should not respond when it changes color (i.e., the red arrow is the stop signal). The task consists of one practice block of 48 trials followed by 3 blocks of 80 trials, with 20 stop-signal trials (25%) in each block. Participants are instructed to respond as quickly and accurately as possible on all trials. However, they are also told that they should only be able to stop their response approximately 50% of the time and they should not slow down to try to be more accurate. Participants had up to 1000 ms to respond while the arrow was on the screen and the inter-trial interval between the offset of one trial and the onset of the next ranged from 750 to 1250 ms. The dependent measure was calculated by subtracting the average stop-signal delay across the 3 blocks (i.e., on stop-signal trials, the time between when a go signal comes on the screen until it

turns into a stop signal) from participants' median reaction time from their distribution of correct go trial reaction times. This outcome measure was multiplied by -1 for reverse-scoring, such that more negative numbers represent worse inhibitory ability.

Tower of London task. Participants completed a computerized version of the Tower of London task (Berg & Byrd, 2002), which was based on the Tower of London task developed by Shallice (1982). During this task, participants are shown a "move" board and a "goal" board on the computer screen, each of which has pegs that are short, medium, and tall, which fit one, two, and three balls respectively. Participants are instructed to move colored balls on the move board using the computer mouse to create a configuration that matches the one shown on the goal board in the fewest number of moves possible. They are also instructed to adhere to the following rules: they are only allowed to move one ball at a time and they cannot move a ball that has another ball on top of it. During the task, trials become progressively more challenging, requiring more moves to complete. The dependent measure used for this task was the total completion time on correct trials, with longer times reflecting greater difficulty with solving trials (e.g., less-planful, more reactive responses). This outcome measure was multiplied by -1 for reverse-scoring, such that more negative numbers represent worse inhibitory ability.

Shifting.

Plus-Minus Task. This paper-pencil task assesses participants' ability to shift flexibility between two different task goals. During this task participants complete three different conditions. The first condition is a baseline assessment involving simple addition. Participants are given a list of 30 two-digit numbers and they must add 1 to each number. The second condition is a baseline assessment involving simple subtraction. Participants are given a second list of 30 two-digit numbers and they must add 1 to each number. The third condition assess shifting ability.

Participants are given a third list of 30 two-digit numbers and they are instructed alternate between adding 1 to and subtracting 1 from the numbers in the list. The three lists of two-digit numbers include numbers from 10 to 99 which were preselected via randomization without replacement. During all three conditions participants are instructed to complete the addition and/or subtraction as quickly as they can without making mistakes. The dependent measure used for this task was calculated by subtracting the average completion time for the two baseline conditions from the completion time for the shifting condition, with higher numbers representing a greater shift cost. This outcome measure was multiplied by -1 for reverse-scoring, such that more negative numbers represent worse shifting ability.

D-KEFS Trail Making Test. This task assesses switching assesses participants' ability to shift flexibility between two different response sets. There are five conditions in this task and each condition is presented using a response form. The second and third conditions assess how long it takes for participants to sequence numbers and letters in order, respectively. The fourth condition is the switching condition (number-letter switching condition). During this condition participants must switch between connecting numbers and letters in order starting at 1 and ending at P (e.g., 1-A-2-B, etc.). This condition is printed on two pages with numbers (1 through 16) and letters (A through P) that are contained within circles. The dependent measure used was the completion time for the number-letter sequencing condition (condition 4) minus the average completion time for the number and letter sequencing conditions (conditions 2 and 3), with higher RTs representing greater difficulty with switching. This outcome measure was multiplied by -1 for reverse-scoring, such that more negative numbers represent worse shifting ability.

D-KEFS Verbal Fluency Test. This task assesses switching assesses participants' ability to shift flexibility between two different verbal response sets. During this task, participants complete two

baseline conditions which assess how quickly individuals can fluidly generate verbal responses based on a specified verbal condition rule. Following the baseline conditions participants complete the category switching condition. During this condition participants must switch between naming types of fruit and types of furniture as quickly as they can within 60 seconds. Participants are instructed not to repeat any items and to shift categories after each item response. The dependent measure used was the total number of successful switches that were made during the category switching condition.

Updating Working Memory.

Spatial Updating. This task assesses updating of spatial WM. During this computer-based task participants are presented with squares in different locations on the computer screen that are serially highlighted, and individuals have to recall the locations of the last 4 highlighted squares. Participants respond by selecting the last 4 highlighted square locations using a computer mouse, in order. Each recall constitutes a trial, and a series of trials comprises a sequence. There are 9 sequences, and the length of each sequence varies from 9 to 13 trials. Participants do not know how many trials will be included in a given sequence. The dependent measure used was the average time required to complete correct trials (RT), which was multiplied by -1 for reverse-scoring, such that more negative numbers represent worse updating ability.

Letter Memory: This task assesses updating of verbal WM. During this computer-based task letters are serially presented to participants every 3 seconds and after each letter presentation participants are prompted to recall the last 4 letters that appear on the screen. Each recall constitutes a trial and a series of trials comprises a sequence. There are 12 sequences and the length of each sequence varies between 9 and 13 trials. Participants do not know how many trials will be included in a given sequence and at the end of each sequence there is a prompt to recall

the last 4 letters again (i.e., an end of sequence recall). The dependent measure used was the proportion of correct end of sequence recalls across all sequences. The highest possible number of correct end-of-sequence recalls is 48 (12 sequences x last 4 letters).

Keep Track: This task assesses updating of verbal WM. During this computer-based task words are serially presented to individuals across 16 trials at a rate of every 1 to 2 seconds. Participants are instructed to keep track of the last word that appeared on screen from specified target categories. At the beginning of each multi-word trial participants are informed which word categories (out of 6 possible) to keep track of. The number of categories that are identified as targets varies from trial to trial (2 to 5 categories), with each category length (2, 3, 4, and 5) occurring 4 times during the task. The length of each trial varies from 15 to 24 words. At the end of each trial participants are prompted to recall the last item they saw from each of the target categories. The dependent measure used was the proportion of the items correctly recalled at the end of each trial. The highest possible number of correct end-of-trial category recalls is 56 (4 trials x 2 categories, 4 trials x 3 categories, 4 trials x 4 categories, and 4 trials x 5 categories).

fMRI.

fMRI Task.

The task utilized was developed by the Heller-Miller Lab. During this task participants press a button as quickly as they can when stimuli are presented on a screen. The stimuli included in the task were positive, negative, and neutral words that were carefully selected on the basis of valence and arousal, which were presented under different motivational conditions of reward, punishment, and non-reward/non-punishment. The motivational conditions were balanced across word type allowing the interactive effects of motivational context and word type to be examined, as well as the main effects of emotion regardless of motivational context (by

collapsing across motivational condition). The present study utilizes the latter approach to examine the main effect of emotion.

Participants first completed a practice block of 24 trials followed by 3 blocks of 48 trials each (144 task trials total; see Figure 3 for representation of trials, p. 75). At the beginning of a trial, participants are shown a cue for 1.5 seconds indicating whether on that trial they can win or lose money, win money only, lose money only or neither win nor lose money. There are an equivalent number of each type of cue (36 each) were included in the task. The cues do not provide information about potential reward or loss magnitude, only that they can potentially gain a reward, be punished, or neither. Following this cue, a fixation dot is presented on screen. All fixation dots are presented for an interstimulus interval that varies between 3-7.5 seconds from trial to trial. After the fixation dot, emotional words are presented for 1.5 seconds. Initially the word is presented in purple ink and changes color after a variable amount of time. Participants are instructed to press a response button as quickly as they can when the word appears on the screen before the word changes color. They are told that if they press the button quickly enough, they will receive the best possible outcome on the trial (e.g., winning money when they can either win or lose). Participants are not informed that the timing between word onset and when it changes colors is optimized on an individual basis such that participants roughly had an equivalent number of successes and failures. Following the word offset an empty box is presented on the screen for 3-7.5 seconds, which afterward changes to indicate whether the participant won money, lost money, neither won nor lost money, or if they had made an error. After the offset of the trial feedback, the trial concludes with another presentation of an empty box which remains on the screen for 3-7.5 seconds.

Word stimuli were selected from the Affective Norms for English Words (ANEW) set (Bradley & Lang, 1999). An equivalent number (48 each) of positive (e.g., joy), negative (e.g., cancer), and neutral words (e.g., statue) were selected on the basis of established norms for arousal, valence, word length, and frequency of use in the English language (Bradley & Lang, 1999; see Table 6, p. 65). Positive and negative words were selected to be equivalent in arousal, and the arousal level for positive and negative words was selected to be higher than that of neutral words. Positive, negative, and neutral words were selected to be similar in word length and frequency of use in the English language. Twelve words of each type (12 positive, 12 negative and 12 neutral) were presented in each motivational condition (reward or punishment, non-reward or punishment, reward or non-punishment, and non-reward or non-punishment). Locally developed MATLAB code was used to control stimuli presentation and to record behavioral responses (version 2009a, The MathWorks Inc., Natick, MA), using Psychophysics Toolbox (version 2.54; Brainard, 1997).

MRI Data Acquisition.

Magnetic resonance data was acquired using a Siemens Magnetom Trio 3T scanner. During the practice block two MPRAGE structural sequences were acquired for registering participants' functional data to standard space (192 axial slices with isotropic spatial extent of 0.9 mm). Gradient field maps were also collected to allow for the correction of geometric distortions in functional data caused by inhomogeneities within the magnetic field (Jezzard & Balaban, 1995). During each of the 3 task blocks 331 functional imaging volumes were collected using a Siemens gradient echo, echo-planar imaging (EPI) sequence (TR 3000 ms, TE 25 ms, flip angle 90°, FOV 256 mm), yielding a total of 993 functional images. Each functional image consisted of 50 oblique axial slices (slice thickness 2.40 mm, in-plane voxel size: 2.13 x 2.13

mm), which was acquired parallel to the plane containing the anterior and posterior commissures.

MRI Data Reduction and Analyses.

MRI processing and statistical analyses were primarily completed using structural and functional tools from the comprehensive analytic software package FSL (FMRIB Software Library; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). Functional data were motion-corrected using MCFLIRT (Motion Correction FMRIB's Linear Image Registration Tool; Jenkinson et al., 2002), temporally filtered with a 1/90 Hz high pass filter, spatially smoothed using a 3-D Gaussian kernel (5 mm full width at half maximum), slice time corrected, and field map corrected. To allow the scanner to reach a steady state, the first 3 volumes collected at the beginning of each task block were discarded.

First-level regression analyses for each block of participants' preprocessed functional time series data was performed using FILM (FMRIB's Improved Linear Model; Woolrich et al., 2001). Statistical maps were computed for each intracerebral voxel using multiple regression. Explanatory variables (EVs) were created for each emotion type (positive, negative, and neutral), collapsing across motivational context. Three predictors of no interest were included to account for performance errors, one modeling each period of the task. Each EV was convolved with a gamma function to approximate the temporal course of the blood-oxygen-level-dependent (BOLD) hemodynamic response function. For each EV, a per-voxel effect-size parameter estimate (β) map representing the magnitude of activation was created for each participant. Functional activation maps for each EV were transformed into MNI stereotactic space using FMRIB's Nonlinear Image Registration Tool (FNIRT). Second-level fixed-effects analyses were carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) to compute the mean

activation for each contrast (e.g., negative versus neutral words) across the three task blocks for each participant.

Next, effects of T1 brain activity on depressive symptoms were examined. Available T2 anhedonic depression scores were utilized, as well as the scores imputed from the MI analyses for participants who did not complete the follow-up session at T2 (e.g., Feusner et al., 2019). The relationships between T1 brain activity and the following independent variables were examined: 1. T1 depressive symptoms, 2. T1 depressive symptoms with T1 anxiety symptoms regressed out ("T1 depression residuals"), 3. T2 depressive symptoms, and 4. T2 depressive symptoms with T1 depressive and anxiety symptoms regressed out ("future depressive symptom residuals"). The use of residual scores to examine the impact of T1 activity on future outcomes controlling for baseline outcomes is a method that is commonly used in longitudinal fMRI studies with a similar design (e.g., Morgan, Olino, McMakin, Ryan, & Forbes, 2013; Telzer, Fuligni, Lieberman, & Galvan, 2014).

Analyses were restricted to a frontal gray matter mask that includes the cingulate cortex and captures regions of interest (DLPFC, ACC, and IFG) based on the Harvard-Oxford probabilistic atlas available in FSL. This mask was used to limit the number of voxels under consideration to help control family-wise error rate. Results were considered significant after correction for multiple comparisons using the threshold-free cluster-enhancement (TFCE) statistic using FSL's randomise tool. This approach returns voxel-wise statistics that take into account cluster size, rather than using an arbitrary threshold for initial cluster formation (Smith & Nichols, 2009). This tool estimates the appropriate threshold for the TFCE statistic to set an overall family-wise error rate of 0.05 and an individual voxel z-threshold of 2.32.

fMRI Behavioral Data.

Average RT was calculated for each word type (positive, neutral, and negative) for each participant, and contrast RTs were created to reflect the fMRI contrasts (negative affect, positive affect, valence, and arousal). RT contrasts were used to predict T2 MASQ-AD8 scores controlling for baseline symptoms of depression and anxiety. Furthermore, RTs were correlated with brain activity that is identified within significant clusters and with neuropsychological assessment measures of inhibition (Color-Word Interference, Stop-Signal, Tower of London tasks, Inhibition Composite, and BRIEF Inhibit).

Time 2 Measures.

At T2, individuals again completed the MASQ-AD. Additionally, participants completed the measures that are not included in present analyses, such as the MASQ-AA, PSWQ, BRIEF and a subset of EF tasks that were administered at T1 (the D-KEFS Color-Word Interference Test, D-KEFS Trail Making Test, and Letter Memory Task).

Addressing Missing Data.

As with Study 1, MI was used to estimate missing T2 data. Prior to MI, a check for systematic differences among individuals who did and did not complete the study at T2 was implemented.

Results

Sample demographics.

One hundred and three participants took part in the study at T1. Fifty-two participants identified their gender as female (51%) and fifty-one identified their gender as male (49%). The majority of participants identified as non-Hispanic or Latino (96%) and identified their race at White (88%), followed by more than one race (6%), Asian (4%), and Black or African American

(2%). Forty-eight individuals (47%) completed the study at T2. The average age of participants at T1 was 19.1 (SD = 1.0) and at T2 was 22.2 years old (SD = 1.0). The average length of time between T1 and T2 was 1,139 days (SD = 97.4), or approximately 3 years and 1 month.

Extreme T1 neuropsychological assessment scores (> 3 SDs from the mean) were set to the value that was 3 SDs away from the mean (Miyake et al., 2000). In total, there were 12 outlier values (SSRT: 0, Stroop: 1, Tower of London: 4, Plus-Minus: 2, Trails: 1, Verbal Fluency: 2, Spatial Updating: 0, Letter Memory: 0, Keep Track: 2).

Potential differences between T2 completers vs. non-completers on T1 variables of interest were examined. No differences were evident at T1 for anhedonic depression, anxious arousal, anxious apprehension, self-reported EF, and task-based EF between those who completed the study and those who did not (Table 7, p. 66). Following imputation, no differences were found between imputed and non-imputed T2 anhedonic depression scores, $t(101) = -1.21$, $p = .229$.

Of the 103 participants that are included in analyses of T1 data, 82 had usable fMRI data at T1 (80%). fMRI data was excluded for individuals who either moved more than one voxel (2.13 mm) between adjacent fMRI volumes, committed errors on 13% or more of the trials, or had poor sMRI and fMRI registration.

Time 1 Self-Reported EF and Current Depressive Symptoms.

Zero-order correlations revealed that poorer self-reported inhibition, shifting, and WM at T1 were associated with higher levels of depressive symptoms at T1 (see Table 8, p. 67). Three separate hierarchical regressions were performed to examine whether the relationship between self-reported EF (inhibition, shifting, and WM, respectively) and T1 depressive symptoms remains after controlling for T1 symptoms of anxiety. The T1 MASQ-AA and PSWQ scores

were entered as predictors into step 1 and self-reported EF in step as a predictor of T1 MASQ-AD8 scores. Each BRIEF subscale predicted T1 depressive symptoms beyond the impact of initial anxiety symptoms, Inhibit: total R^2 = .41, ΔR^2 = .07, *B* = .26, *F-change* (1, 99) = 9.70, *p* = .002, Shift: total R^2 = .45, ΔR^2 = .12, *B* = .43, *F-change* (1, 99) = 21.43, *p* < .001, and WM: total R^2 = .45, ΔR^2 = .09, *B* = .34, *F-change* (1, 99) = 16.94, *p* < .001.

Time 1 Task-based EF and Current Depressive Symptoms.

There was a significant negative association between performances on the Tower of London (inhibition) and T1 depressive symptoms (see Table 9, p. 68). After controlling for the impact of T1 anxious arousal and anxious apprehension in step 1 of a hierarchical regression, the Tower of London continued to predict a significant portion of variance in T1 depressive symptoms, total R^2 = .41, ΔR^2 = .06, *B* = -.24, *F-change* (1, 99) = 9.39, *p* = .003. Additionally, the Inhibition Composite emerged as a significant predictor of T1 depressive symptoms above T1 anxiety, total R^2 = .38, ΔR^2 = .03, *B* = -.17, *F-change* (1, 99) = 4.70, *p* = .033. Letter Memory (updating) also predicted current depression above T1 anxiety, but the relationship with Letter Memory was not in the expected direction, total R^2 = .38, ΔR^2 = .03, *B* = .16, *F-change* (1, 99) = 4.19, *p* = .043.

Time 1 Self-Reported EF and Future Depressive Symptoms.

Zero-order correlations revealed that poorer self-reported inhibition, shifting, and WM at T1 were associated with higher levels of depressive symptoms at T2 (see Table 8, p. 67). Three separate hierarchical regressions were performed to examine whether the relationship between self-reported EF (inhibition, shifting, and WM, respectively) and T2 depressive symptoms remained after controlling for T1 symptoms of depression and anxiety. The T1 MASQ-AD8, MASQ-AA and PSWQ scores were entered as predictors into step 1 and self-reported EF was

entered as a predictor into step 2. Both inhibition and WM predicted future depressive symptoms above psychopathology symptoms at T1, Inhibit: total R^2 = .47, ΔR^2 = .11, *B* = .37, *F-change* (1, 98) = 19.45, $p < .001$ and WM: total R^2 = .41, ΔR^2 = .04, *B* = .23, *F-change* (1, 98) = 6.14, p = .015, whereas shifting did not, total R^2 = .37, $\Delta R^2 < .01$, *B* = -.01, *F-change* (1, 98) = .01, p = .939.

Time 1 Task-based EF and Future Depressive Symptoms.

There were significant negative associations between performances on the Stop Signal (inhibition), Keep Track (updating), and Letter Memory (updating) tasks and T2 depressive symptoms (see Table 9, p. 68). The association between the Updating Composite and T2 depressive symptoms was also significant. After statistically controlling for the impact of T1 psychopathology symptoms in step 1 of a hierarchical regression, the Stop Signal, Keep Track, and Letter Memory tasks continued to predict T2 depressive symptoms, Stop Signal: total R^2 = .40, ΔR^2 = .03, *B* = -.18, *F-change* (1, 98) = 5.12, p = .026, Keep Track: total R^2 = .41, ΔR^2 = .04, *B* = -.21, *F-change* (1, 98) = 7.04, p = .009, Letter Memory: total R^2 = .44, ΔR^2 = .07, *B* = -.28, *F-change* (1, 98) = 12.69, p = .001. Furthermore, the Updating Composite measure accounted for a significant portion of variance in T2 depressive symptoms after controlling for T1 psychopathology symptoms, total R^2 = .43, ΔR^2 = .06, *B* = -.24, *F-change* (1, 98) = 9.83, p = .002, whereas the Inhibition Composite was marginally significant, total R^2 = .39, ΔR^2 = .02, *B* = -.16, *F-change* (1, 98) = 3.92, p = .051. A summary of the self-reported EF and task-based assessment results is included in Table 10 (p. 69).

Self-reported and Task-Based Measures of EF.

As shown in Table 11 (p. 70), BRIEF subscales did not strongly correlate with task-based measures of EF. The only significant association that emerged was between BRIEF WM and the updating WM composite, $r(101) = -.24$, $p = .016$.

Alternative EF Analyses

The confirmatory factor analysis revealed that the Madian et al. (in press) single-factor model ("general EF") provided a good fit for the data (χ^2 $p = 0.118$; RMSEA = 0.054; CFI = 0.913). General EF did not predict T1 depressive symptoms, even after accounting for co-occurring symptoms of anxiety ($B = .01$, $p = .896$). Although general EF did not predict T2 depressive symptoms ($B = -.18$, $p = .101$), it did predict future depressive symptom after taking variance associated with anxiety into account ($B = -.20$, $p = .024$).

fMRI.

RT and Depressive Symptoms.

Behavioral performance was not significantly correlated with T1 depressive symptoms for any of the contrasts, even after accounting for co-occurring symptoms of anxiety. Behavioral performance was also not significantly related to T2 depressive symptoms. Although there was a trend toward RT for the valence contrast and future depressive symptoms after controlling for baseline symptoms of depression and anxiety, $r(80) = .18$, $p = .100$, results did not reach statistical significance.

RT and Neuropsychological Assessment Performance.

No significant associations emerged between the RT contrasts and any of the inhibition measures. Additionally, no significant associations emerged for general EF.

Neural Activity and Depressive Symptoms.

Analyses, which were restricted to the frontal lobe and the cingulate cortex, indicated T1 depressive symptoms did not predict T1 neural activity for any of the contrasts. These results did not change after controlling for T1 anxious arousal and anxious apprehension. Significant relationships were evident between T1 neural activity and depressive symptoms at T2 and for several contrasts, after controlling for baseline symptoms of depression and anxiety (see Table 12, pp. 71-72). Specifically, higher T2 depression residuals predicted lower activity for positive relative to negative words in the right frontal pole, orbitofrontal cortex (OFC), right ventrolateral prefrontal cortex (vlPFC), right ventromedial prefrontal cortex (vmPFC), paracingulate gyrus, dorsal anterior cingulate cortex (dACC), middle cingulate cortex (MCC), rostral anterior cingulate cortex (rACC), superior frontal gyrus (SFG), right middle frontal gyrus (MFG, including DLPFC), and right inferior frontal gyrus (IFG) pars triangularis (see Figure 4, p. 76). Higher T2 depression residuals also predicted lower activity for high- relative to low-arousing words in the right SFG and MFG (including DLPFC; see Figure 5, p. 76). Finally, higher T2 depression residuals predicted lower activity for positive relative to neutral words in bilateral frontal pole, right OFC, right vlPFC, left vmPFC, bilateral SFG, bilateral MFG (including DLPFC), right precentral gyrus (see Figure 6, p. 77).

Neural Activity and RT

For the valence contrast, lower activity in the dACC (Figure 4, box G, p. 76) predicted slower RT for positive than negative words, $r(80) = -.22$, $p = .043$ (see Figure 7, p. 78). No other significant associations emerged.

Neural Activity and Neuropsychological Assessment Performance.

Associations between neural activity in brain regions that were significantly related to T2 depressive symptom residuals and self-reported and task-based measures of inhibition were explored. For the valence contrast, less activity in the right vmPFC (Figure 4, box L, p. 76) predicted poorer self-reported inhibition, $r(80) = -.25$, $p = .021$ (see Figure 8, pg. 79). No significant associations emerged for general EF.

Neural Activity, Negative Affect, and Future Depressive Symptoms.

Neural activity was not significantly related to future depressive symptoms or residual depressive symptom among those with high levels of negative affect at baseline.

Clinical Interview.

As shown in Table 13 (p. 73), approximately 40% of percent of individuals assessed via SCID had a lifetime history of a mental health disorder. The most common lifetime diagnoses were major depressive disorder (13%) and alcohol abuse disorder (13%). Only one participant met full criteria for a current major depressive episode at the T2 assessment, which was related to a diagnosis of Bipolar I. No participants met criteria for a psychotic disorder.

Discussion

Results of Study 2 indicate support for the hypothesis that EF deficits predict current and future symptoms of depressive symptoms. With regard to current depressive symptoms, poorer self-reported EF broadly predicted higher levels of depressive symptoms, and these associations were large in size. After accounting for co-occurring anxiety, poorer inhibition, shifting, and WM continued to predict depressive symptoms.

In contrast with the broad associations between current depressive symptoms and the BRIEF, current depressive symptoms were associated with poorer performance on only 1 of the

9 EF tasks (an inhibition task) and marginally for the inhibition composite. The relationship between current depressive symptoms and inhibition, as indicated by performance on the Tower of London task, was approaching medium in size. After accounting for co-occurring anxiety, current depressive symptoms predicted performance on 2 of the 9 EF tasks, and a significant association with the inhibition composite measure emerged. General EF was not significantly related to current depressive symptoms, even after controlling for anxiety. During the fMRI task, which was designed to assess inhibitory functioning in the context of emotional distraction, current depressive symptoms did not predict behavioral performance or neural activity.

Although relationships between broad EF deficits and current depression have commonly been reported among adults with DSM-based depression, individuals with major depression tend to be more consistently impaired on measures of inhibitory functioning than other EF measures, with effect sizes typically around $d = .70$. Notably, the largest effect size for any measure in the Snyder (2013) meta-analysis emerged for an inhibition task (the Hayling task, $d = .97$), suggesting that inhibitory deficits are particularly prominent in current depression. In line with this, Bredemeier et al. (2016) found that current depressive symptoms, as measured by current major depressive episode DSM symptom count, was associated with poorer task-based EF inhibition, but not shifting. Although in the present study relationships emerged between current depressive symptoms and self-reported and task-based inhibition, no associations were found between current depressive symptoms and neural activity during the emotion-word portion of the fMRI task. This suggests that either inhibition processes are not strongly tapped by the fMRI task or that individuals were able to engage in compensatory strategies during the task.

With regard to future depressive symptoms, poorer self-reported EF at T1 broadly predicted higher levels of future depressive symptoms. After statistically controlling for the

impact of baseline psychopathology symptoms, poorer self-reported inhibition and WM remained significant predictors. Additionally, future depressive symptoms were predicted by performance on 3 out of the 9 tasks (one inhibition task and two updating tasks), as well as the updating WM composite. The inhibition composite marginally predicted future depressive symptoms (p = .051). Most of these associations were approaching medium in size and all relationships remained after accounting for baseline symptoms of depression and anxiety.

Using an alternative analytical approach for the task-based measures, poorer general EF performance predicted future depressive symptoms after accounting for depression and anxiety at T1. Despite a relationship with general EF, future depressive symptoms were not significantly associated with either self-reported or task-based shifting. It is notable, however, that there are inconsistencies across previous studies, with self-reported shifting deficits appearing to predict future depressive symptoms more consistently than task-based measures (e.g., Dickson et al., 2016; Rudolph et al., 2017). Taken together, results support the supposition that higher future depressive symptoms are related to poorer EF in multiple domains, which is indicative of broad deficits, although deficits do not appear to be evident for all EF domains.

In addition to the relationships between future depressive symptoms and measures of EF, neural activity during the fMRI task predicted future depressive symptoms after accounting for T1 symptoms of depression and anxiety. Specifically, for positive relative to negative words, lower activity within several regions, including the right DLPFC, right IFG, right and medial OFC, dorsal and rostral ACC, and right anterior PFC, predicted higher levels of future depressive symptoms. Higher levels of future depressive symptoms were also predicted by lower activity in the right DLPFC for high arousing relative to neutral words, and by lower activity in the left and right DLPFC, medial OFC, and left and right anterior PFC for positive relative to neutral words.

A relationship between lower right DLPFC activity and higher levels of future depressive symptoms was evident across the valence, arousal, and PA contrasts. Right DLPFC has been found to play an important role in top-down regulation of attention, including sustained attention and attentional shifting (Coull, Frackowiak, & Frith, 1998; Fassbender et al., 2006; Häger et al., 1998). In healthy controls, anodal (excitatory) transcranial direct current stimulation applied to the right DLPFC led to difficulty disengaging from both positive and negative stimuli, highlighting a role in attentional control that is not valence specific (Sanchez, Vanderhasselt, Baeken, & De Raedt, 2016). Indicative of a role in "cold cognition," reduced right DLPFC activity was evident among individuals with depression during a non-emotional Go/No-Go task, and poorer SSRI treatment responsivity was predicted by lower right DLPFC activity at T1 (Gyurak et al., 2016). Although individuals with depression may have broad difficulty with attention regulation, results of Study 2 were specific to positive stimuli, indicating that individuals who go on to develop higher levels of depressive symptoms have initial difficulty sustaining attention in the context of positive information.

It was also initially hypothesized that the ACC would exhibit hyperactivity in the context of negative relative to positive stimuli at T1, that this hyperactivity would be driven by enhanced processing of negative information, and that it would predict depressive symptoms. In contrast, hypoactivity in the ACC in this region predicted future depression. The dACC plays an important role in conflict monitoring and error detection, and it is a central node of the salience network (SN). The SN, which includes several regions such as the anterior PFC, is thought to monitor internal and external events and to coordinate behavioral responses to relevant stimuli, especially in the context of distractors and need for behavioral change (Barrett & Satpute, 2013). In the face of distraction from goals (i.e., conflict), dACC activity supports task performance by

signaling a need for greater top-down control of behavior via the DLPFC (Banich, 2009). According to the cascade-of-control model, the DLPFC imposes a task set and the dACC modulates the degree of control that is needed to help achieve task-relevant goals (Banich, 2009). In the present study, the dACC was activated less for positive than negative stimuli, and lower dACC activity significantly predicted slower RT for positive versus negative stimuli. Findings thus demonstrate a direct link between reduced neural activity and poorer performance on the task for positively-valenced stimuli.

Aberrant dACC activity has been reported in depression (for a discussion, see Nitschke & Mackiewicz, 2005; Smoski et al., 2009) and deficient functional coupling between left DLPFC and dACC has been reported for individuals with high levels of depressive symptoms, suggestive of a disruption in the compensatory support that the dACC provides to help individuals achieve task goals (Silton et al., 2001). Reduced dACC activity has been purported to contribute to deficits in volitional activity, leading to difficulty in implementing goal-directed behavior (Nitschke & Mackiewicz, 2005). Reflecting the importance of dACC functioning for volitional activity, reduced dACC activity for reward stimuli among individuals with depression predicted poorer treatment response to a behavioral activation intervention (Carl et al., 2016). Reduced dACC activity in the present study thus appears to reflect inefficient support of goal-directed behavior in the context of positive relative to negative stimuli.

Reduced activity in the right IFG was also evident within the valence contrast for positive relative to negative words. Right IFG has been found to be active across several inhibitory control tasks, including the Stop Signal and Stroop tasks (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010; Rubia, Smith, Brammer, & Taylor, 2003), and damage to the right IFG disrupts inhibitory functioning (Aron et al., 2003). However, reduced right IFG activity in the

present study did not predict difficulty on any of the inhibition tasks or the self-reported inhibition measure, suggesting that this reduction in activity did not translate into ineffective inhibitory performance. A plausible alternative explanation is that reduced right IFG activity reflected a reduced need to inhibit interference, since positive words failed to capture attention and therefore did not directly interfere with task performance.

In contrast with right IFG activity, decreased vmPFC activity for positive relative to negative stimuli predicted greater self-reported inhibition deficits in daily life. Broadly, the vmPFC is involved inhibiting emotional information and regulating the amygdala (for review, see Etkin, Egner, & Kalisch, 2011). In cross-sectional studies, reduced activity in the vmPFC, especially within the right hemisphere, has been found to impair decision making and social behavior (Tranel, Bechara, Denburg, 2002), and lower levels of global connectivity between the vmPFC and other brain regions predict greater depression symptom severity (Murrough et al., 2016). It is possible that impaired social decision making, reflected in reduced activity in this region, may impact behaviors that are captured by the self-reported inhibition measure, such as difficulty waiting in line or making inappropriate comments.

Additional reductions in neural activity that were evident within both the valence and PA contrasts in the context of positive stimuli occurred within regions associated with reward processing and decision-making, including the OFC. Broadly, anhedonia, which is a core feature of depression, is associated with impairment in reward anticipation, consumption, and learning (for a review, see Der-Avakian & Markou, 2012; Keller et al., 2013). Among individuals with high levels of trait anhedonia, disrupted anticipation of reward is characterized by reduced activity of the OFC, ACC, and medial PFC (Der-Avakian & Markou, 2012). The OFC is a crucial hub for reward processing and decision-making and performs several functions, including

the representation of current reward stimulus value and prediction of future reward value (for review, see O'Doherty, 2007). Information regarding reward value is projected from the OFC to the ACC to calculate information about effort needed to obtain a reward, which is then projected to the vmPFC and DLPFC (Der-Avakian & Markou, 2012).

With regard to depression, blunted reward processing is a common finding. Notably, across reward-related processes, such as anticipation, consumption, and reinforcement learning, individuals with depression exhibit hypoactivation of striatal regions (e.g., nucleus accumbens) and cortical regions (e.g., OFC and ACC), and reduced cortical-striatal connectivity (for reviews, see Admon & Pizzagalli, 2015 and Eshel & Roiser, 2010). Aberrant reward processing has also been found among young adults without a history of depression who have a parent with a history of depression, characterized by reduced OFC and ACC activity in response to rewarding stimuli compared to controls (McCabe, Woffindale, Harmer, & Cowen, 2012). In addition to parental history, peer victimization in adolescence is associated with altered reward processing, with greater peer victimization in early adolescence predicting lower medial PFC responsivity to reward in later adolescence (Casement et al., 2013). Among never-depressed adolescents, disrupted reward processing has been found to prospectively predict higher levels of depressive symptoms and the development of major depressive episodes (Bress, Foti, Kotov, Klein, & Hajcak, 2013; Morgan, Olino, McMakin, Ryan, & Forbes, 2013). Taken together, present results indicate that altered reward processing is not merely a product of current depressive symptoms, and that altered reward processing foreshadows future depression. Given that aberrant neural activity emerged within brain regions known to be involved in EF and reward processing in the present study, combined difficulties with these processes may be especially impairing. It will be

important to examine the impact of EF on future depressive symptoms within different motivational contexts (e.g., reward versus punishment) in a future study.

A notable limitation of Study 2 is that the emotion-word portion of the fMRI task does not appear to tap strongly into inhibitory processes. Although it was anticipated that the emotion words would distract individuals from task-goals and therefore require inhibitory process to overcome distraction, depressive symptoms were not significantly associated with difficulties disengaging from stimuli according to RT measures and neural activity. It is possible that inhibitory processes were not strongly recruited because there was no direct conflict between word color and meaning. Although the fMRI task may not have strongly tapped into inhibition per se, it did appear to measure aspects of EF, as multiple brain regions known to be involved in EF were underactive in the context of positive words. In the future, other fMRI studies should be implemented to assess the predictive relationship of neural activity on future depressive symptoms during tasks that are optimized to assess inhibition.

Another limitation of Study 2 concerns the clinical assessment. Because the clinical assessment was not completed prospectively, it was not possible to determine how many participants met criteria for Major Depressive Disorder, since not all participants completed the study at T2. An additional challenge was that several participants who completed the study had difficulty recalling with precision the exact dates of their past major depressive episodes. Even if follow-up analyses were conducted by excluding individuals with suspected depression prior to T1, the sample size of individuals with T2 SCID data is not sufficiently large enough to draw firm conclusions from the results.

Results of Study 2 indicate that, among individuals at risk for internalizing psychopathology, difficulties with inhibition are predictive of current depressive symptoms, and

broader difficulties with updating WM and general EF are predictive of future depressive symptoms. This suggests that different aspects of EF impact current relative to future depressive symptoms. Inhibitory processes have been found to be especially important for social and adaptive functioning (Vuontela et al., 2012), which may, in part, explain why inhibition tends to be commonly associated with depression. Although broad deficits reportedly impacted functioning in daily life (as reflected in the relationship between self-reported EF and current depressive symptoms), a more significant impact of broad deficits on functioning and resultant hopelessness that contributes to depression may emerge over time. It will be critical to continue to investigate how this process unfolds, as disrupting this process may serve to reduce depression risk.

Results also indicate that future, but not current, depressive symptoms are predicted by reduced engagement with positive information relative to negative and neutral information, though only after accounting for the impact of anxiety at baseline. Comorbid depression and anxiety are often associated with greater functional impairment than a single depressive or anxiety-related disorder. However, present results suggest that anxiety symptoms may, in some cases, support cognitive processing. In line with this, individuals with major depression without comorbid panic disorder were found to exhibit aberrant (i.e., impaired) dACC activation during reward anticipation, whereas activation did not differ between controls and participants with comorbid major depression with panic disorder (Gorka et al., 2014). In another study, Engels et al. (2010) found that while depressive symptoms predicted reduced left DLPFC activation for negative relative to neutral words, this depended on the degree of co-occurring anxiety. Specifically, when anxious apprehension was high, reduced left DLPFC activity was no longer evident (Engels et al., 2010). It will be important for future studies to explore the impact of

different dimensions of co-occurring anxiety (e.g., anxious arousal and anxious apprehension) on EF, and how the impact of these dimensions on EF confers risk for depression.

CHAPTER 4: GENERAL DISCUSSION

Overall, the results of Study 1 and Study 2 suggest that at least some EF deficits predict current and future depressive symptoms. Although updating WM predicted current depressive symptoms in Study 1 and it was anticipated that this reflected broad EF deficits, this was not corroborated in Study 2, as it was task-based inhibition that predicted current depressive symptoms. One reason that task results may have been inconsistent across studies is that the n-back task does not appear to be a specific measure of updating WM. Freidman et al. (2008) found that in the context of a the three-factor EF model, a spatial 2-back task loaded least strongly onto the Updating factor (.46 versus .65 and .66). Within a nested factors model, the 2-back task loaded onto the Common EF factor more than the Updating Specific factor (.37 versus .22), which was not the case for Keep Track (.41 versus .54) or Letter Memory (.44 versus .53). Given these findings and that current depressive symptoms were predicted by measures of inhibition in Study 2, it is possible that the results of Study 1 reflect an association with inhibition rather than updating WM. If so, this would provide further evidence that inhibition deficits contribute to current depressive symptoms.

For both Study 1 and Study 2, relationship specificity between self-reported EF domains and depressive symptoms did not emerge. In general, current depressive symptoms were associated with all of the BRIEF subscales, even after accounting for co-occurring symptoms of anxiety. Future depressive symptoms were also related to all BRIEF subscales, although broad deficits did not hold after accounting for baseline symptoms of depression and anxiety. Across both studies, associations between the BRIEF measures and task-based measures were generally small in size. For Study 1, correlations between n-back accuracy and the BRIEF subscales were all significant, but only ranged from r = -.15 to -.18. For Study 2, associations between the

composite EF measures and BRIEF subscales ranged from r = -.003 to -.24, with only one significant association emerging between BRIEF WM and the updating WM composite. Because the BRIEF subscales do not appear to strongly map onto specific aspects of EF, claims about specific relationships between EF domains and future depressive symptoms on the basis of the BRIEF should be interpreted cautiously.

A notable limitation of both studies was the high rate of non-completers in both studies (64% and 47% in Study 1 and 2, respectively). Although the data imputation method used in the present studies has been found to be robust even for 60-70% of missing data, it will be important to replicate present analyses with samples that have fewer dropouts. Although several strategies that are known to enhance participant retention were utilized in both studies (e.g., online participation options, participation incentives, and reminders), the use of additional strategies, such as the development of a website devoted to the longitudinal project and enhanced monetary incentives, may increase the likelihood of participant retention (Abshire et al., 2017).

Another limitation of both studies concerns the use of averaged scores from the task-based assessments to capture the three-factor model of EF. Study 2 used tasks that varied in modality for each EF processed (e.g., visuospatial, verbal), and thereby increased the likelihood that modality alone did not drive the effects. However, many sources of variance remain within composite measures, making it difficult to identify whether EF processes or other sources of shared variance were driving the effects. Although the use of latent factors does not eliminate this issue and there is not an agreed-upon way to parse EF processes, latent approaches capture both shared and unique sources of variance, thereby assessing relationships with greater precision (Miyake et al., 2000; Snyder et al., 2015).

In the future, it will be important to continue to examine whether EF deficits predict future depressive symptoms broadly, or whether this is primarily the case for individuals at risk for depression (e.g., based on trait affect or family history of depression). If risk for internalizing psychopathology and/or depression is an important moderator of the impact of EF on the course of depression, then it will be more cost-effective to devote resources to try to target EF within this population. An important related question is how to best target EF deficits. Although targeting EF directly could be helpful, the literature has been mixed regarding its effectiveness of EF training. Although some computerized training programs have been found to improve performance on EF tasks, this is often limited to the EF skills that are trained (Diamond & Lee, 2011). More indirectly, mindfulness meditation and exercise programs have been found to enhance EF processes (Diamond & Lee, 2011; Heeren, Van Broeck, & Philippot, 2009; for review, see Tang, Yang, Leve, & Harold, 2012), and exercise is an option that is generally available for most individuals. Because trauma has been found to impact cognitive functioning and EF, early trauma-processing may also help to prevent the development of persistent EF deficits that could contribute to future depression.

TABLES

Table 1. Results of meta-analyses that have examined the associated between inhibition, shifting, updating WM, and DSM-diagnosed clinical depression.

EF Process	**Study**	**Measure**	**Results (MDD vs. Controls)**
Inhibition	Epp et al. (2012)	Stroop Interference RT	Hedges' g = .89
	Snyder (2013)	Stroop Interference RT	*d* = .39
		Stroop Incongruence Accuracy	*d* = .70
Shifting	Snyder (2013)	WCST	*d* = .47
		Trail Making Test B	*d* = .59
		ID/ED	*d* = .46
	Lee et al. (2012) - first MDE	Trail Making Test B	Hedges' g = .22
		WCST, Modified WCST, & ID/ED	Hedges' g = .53
	Rock et al., (2014)	ID/ED	
		Currently depressed	*d* = .44
		Currently depressed, unmedicated	*d* = .09
Updating WM	Snyder (2013)	Digit Span Backward	*d* = .55
		Visuospatial Span Backward	*d* = .72
		n-back	*d* = .63
	Lee et al. (2012) - first MDE	Digit Span Backward & Visuospatial Span Backward	Hedges' g = .16
	Rock et al., (2014)	Spatial WM - Errors	
		Currently depressed	*d* = .54
		Currently depressed, unmedicated	*d* = .46

Table 2. Results of meta-analyses that have examined the associated between inhibition, shifting, updating WM, and remitted DSM-diagnosed clinical depression.

EF Process	**Study**	**Measure**	**Results (Remitted MDD vs. Controls)**
Inhibition	Bora et al. (2012)	Stroop Interference RT	*d* = .74
Shifting	Rock et al. (2014)	ID/ED	*d* = .53
	Bora et al. (2012)	Trail Making Test B - RT	*d* = .48
		WCST - Perseverative Errors	*d* = .18
		WCST - Categories Achieved	*d* = .30
Updating WM	Bora et al. (2012)	Digit Span Backward	*d* = .41
	Rock et al., (2014)	Spatial WM	*d* = .53

Table 3. Study 1. Questionnaire scores and task performance results for completers and non-completers.

N = 454	**Completed T1 & T2 (Completers) N = 164** Mean (SD)	**Completed T1 Only (Non-completers) N = 290** Mean (SD)	**t-test**
Psychopathology Symptoms			
T1 MASQ-AD8	16.40 (5.1)	16.71 (5.0)	t(452) = -.64, *p*=.526
T1 MASQ-AA	27.20 (7.2)	27.62 (8.0)	t(452) = -.55, *p*=.580
T1 PSWQ	51.15 (14.18)	50.91 (14.2)	t(452) = .18, *p*=.859
Self-reported EF			
BRIEF Inhibit	13.17 (2.9)	13.44 (3.2)	t(452) = -.90, *p*=.369
BRIEF Shift	9.62 (2.5)	9.88 (2.7)	t(452) = -.1.04, *p*=.300
BRIEF WM	13.15 (3.2)	13.24 (3.4)	t(452) = -.28, *p*=.777
WM Task (Accuracy)			
Verbal 2-Back	73.85 (22.1)	73.85 (24.3)	t(452) = .02, *p*=.985
Spatial 2-Back	72.67(18.0)	72.98 (19.7)	t(452) = -.31, *p*=.754

MASQ-AD = Mood and Anxiety Symptom Questionnaire, 8-item Anhedonic Depression Subscale; MASQ-AA = Mood and Anxiety Symptom Questionnaire, Anxious Arousal Subscale; PSWQ = Penn State Worry Questionnaire; EF = Executive Function; BRIEF = Behavior Rating Inventory of Executive Function, Adult Version; WM = Working Memory

Table 4. Descriptive statistics for Study 1.

N = 355	**Final Sample** Mean (SD)
Psychopathology Symptoms	
T1 MASQ-AD8	16.60 (5.1)
T1 MASQ-AA	27.47 (7.7)
T1 PSWQ	51.00 (14.2)
T2 MASQ-AD8	15.71 (5.1)
Self-reported EF	
BRIEF Inhibit	13.35 (3.1)
BRIEF Shift	9.79 (2.6)
BRIEF WM	13.35 (3.1)
WM Task (Accuracy)	
Verbal 2-Back	73.82 (23.5)
Spatial 2-Back	71.91 (22.0)

MASQ-AD = Mood and Anxiety Symptom Questionnaire, 8-item Anhedonic Depression Subscale; MASQ-AA = Mood and Anxiety Symptom Questionnaire, Anxious Arousal Subscale; PSWQ = Penn State Worry Questionnaire; EF = Executive Function; BRIEF = Behavior Rating Inventory of Executive Function, Adult Version; WM = Working Memory

Table 5. Study 1. Pearson product moment correlation coefficients for time 1 self-reported EF, task-based updating working memory performance, and time 1 and time 2 depressive symptoms.

N=355	**T1 MASQ-AD8**	**T2 MASQ-AD8**	**BRIEF Inhibit**	**BRIEF Shift**	**BRIEF WM**	**n-back Accuracy**
T1 MASQ-AD8	-	.55**	**.38****	**.42****	**.34****	**-.18****
T2 MASQ-AD8	-	-	**.22****	**.33****	**.28****	**-.16****
BRIEF Inhibition	-	-	-	.50**	.66**	**-.16****
BRIEF Shifting	-	-	-	-	.59**	**-.15****
BRIEF WM	-	-	-	-	-	**-.18****

*p<.05
**p<.01

Table 6. Study 2. Characteristics of the word stimuli from the iStroop task. This table is included in Infantolino et al. (unpublished manuscript).

Word Characteristics	Positive Words	Neutral Words	Negative Words
Average Arousal	6.59	3.73	6.56
Average Valence	7.80	5.23	2.49
Average Frequency	51.50	51.81	51.98
Average Word Length	5.78	5.33	5.38

Word stimuli were selected from the Affective Norms for English Words (ANEW) set (Bradley & Lang, 1999). (ANEW) set (Bradley & Lang, 1999). Arousal and valence data from the ANEW set are measured on a scale ranging from 1 to 9, with 9 corresponding to the most arousing and pleasant ratings, respectively. Frequency information was obtained from Toglia and Batting (1978).

Table 7. Study 2. Questionnaire scores and task performance results for study completers and non-completers.

N=103	**Completed T1 & T2 (Completers) N = 48**	**Complete T1 Only (Noncompleters) N = 55**	**t-test**
Psychopathology Symptoms			
T1 MASQ-AD8	15.65 (4.0)	15.70 (5.1)	t(101) = -.06, *p*=.956
T1 MASQ-AA	23.42 (5.9)	24.41 (6.6)	t(101) = -.79, *p*=.431
T1 PSW	45.47 (13.3)	48.41 (16.1)	t(101) = -1.00, *p*=.318
Self-reported EF			
BRIEF Inhibit	12.92 (2.5)	13.45 (3.3)	t(101) = -.91, p=.364
BRIEF Shift	9.46 (2.7)	9.53 (3.0)	t(101) = -.12, p=.904
BRIEF WM	11.81 (3.5)	12.47 (3.3)	t(101) = -.98, p=.327
EF Tasks (*reverse scored)			
Stroop Inhibition RT*	40.21 (7.4)	40.62 (7.6)	t(101) = .28, p=.783
Stop Signal RT*	217.27 (28.2)	219.77 (32.5)	t(101) = .41, p=.679
Tower of London RT*	250.20 (76.2)	248.32 (70.0)	t(101) = -.13, p=.897
Plus-Minus Shift Cost*	14.02 (10.2)	14.92 (10.8)	t(101) = .43, p=.667
Trails Switch RT*	51.28 (13.9)	53.40 (12.5)	t(101) = .79, p=.433
Verbal Fluency Switch	14.81 (2.5)	15.51 (3.3)	t(101) = 1.20, p=.234
Spatial Updating RT*	706.87 (97.4)	718.09 (108.3)	t(101) = .55, p=.584
Keep Track Accuracy	77.54 (14.0)	81.03 (13.2)	t(101) = 1.30, p=.197
Letter Memory Accuracy	80.08 (7.0)	78.29 (7.8)	t(101) = -1.22, p=.225

MASQ-AD8 = Mood and Anxiety Symptom Questionnaire, 8-item Anhedonic Depression Subscale; MASQ-AA = Mood and Anxiety Symptom Questionnaire, Anxious Arousal Subscale; PSWQ = Penn State Worry Questionnaire; BRIEF = Behavior Rating Inventory of Executive Function, Adult Version

Table 8. Study 2. Pearson product moment correlation coefficients for time 1 self-reported EF measures and time 1 and time 2 depressive symptoms.

N = 103	**BRIEF Inhibit**	**BRIEF Shift**	**BRIEF WM**
T1 MASQ-AD8	**.44****	**.62****	**.54****
T2 MASQ-AD8	**.51****	**.31****	**.42****
BRIEF Inhibit	-	.50**	.69**
BRIEF Shift	-	-	.71**
$^{*}p<.01$			

Table 9. Study 2. Pearson product moment correlation coefficients for time 1 task-based EF measures and time 1 and time 2 depressive symptoms.

I. Task-Based Measures of Inhibition				
N=103	**Stroop Inhibition**	**Stop Signal**	**Tower of London**	**Inhibition Z-score Composite**
T1 MASQ-AD8	-.02	-.10	**-.25***	-.19
T2 MASQ-AD8	-.12	**-.24***	.00	-.19
II. Task-Based Measures of Shifting				
N=103	**Plus-Minus**	**Trails**	**Verbal Fluency**	**Shifting Z-score Composite**
T1 MASQ-AD8	-.07	-.06	-.03	-.08
T2 MASQ-AD8	.06	.05	.08	.09
III. Task-Based Measures of Updating				
N=103	**Spatial Updating RT**	**Letter Memory**	**Keep Track**	**Updating Z-score Composite**
T1 MASQ-AD8	**-.21***	-.04	.15	-.05
T2 MASQ-AD8	-.13	**-.21***	**-.29****	**-.30****

*p<.05
**p<.01

Table 10. Summary of self-reported and task-based EF results for Study 1 and Study 2.

	T1 MASQ-AD8	T1 MASQ-AD8 Above T1 Anxiety?	T2 MASQ-AD8	T2 MASQ-AD8 Above T1 Anxiety & Dep?
Study 1 (N=355)				
BRIEF Inhibit	*	*	*	n.s.
BRIEF Shift	*	*	*	*
BRIEF WM	*	*	*	n.s.
n-Back Accuracy	*	*	*	n.s.
Study 2 (N=103)				
BRIEF Inhibit	*	*	*	*
BRIEF Shift	*	*	*	n.s.
BRIEF WM	*	*	*	*
Inhibition Composite	*p*=.051	*	*p*=.058	*p*=.051
Shifting Composite	n.s.	*p*=.064[a]	n.s.	n.s.
Updating Composite	n.s.	n.s.	*	*
Stroop Inhibition RT	n.s.	n.s.	n.s.	n.s.
Stop Signal RT	n.s.	n.s.	*	*
Tower of London RT	*	*	n.s.	n.s.
Plus-Minus Shift Cost	n.s.	n.s.	n.s.	n.s.
Trails Switch RT	n.s.	n.s.	n.s.	n.s.
Verbal Fluency Shift	n.s.	*p*=.062[a]	n.s.	n.s.
Spatial Updating Acc	*p*=.051	n.s.	*p*=.066	n.s.
Keep Track Acc	n.s.	n.s.	*	*
Letter Memory Acc	n.s.	*[a]	*	*

*: Significant relationship
n.s.: Non-significant relationship
[a]: Relationships were not in the expected direction

Table 11. Study 2. Pearson product moment correlation coefficients for time 1 self-reported and task-based EF scores.

N = 103	**BRIEF Inhibit**	**BRIEF Shift**	**BRIEF WM**	**Inhibition Composite**	**Shifting Composite**	**Updating Composite**
BRIEF Inhibit	-	**.50****	**.69****	-.003	-.04	-.08
BRIEF Shift	-	-	**.71****	-.14	-.05	-.10
BRIEF WM	-	-	-	-.11	-.17	**-.24***
Inhibition Composite	-	-	-	-	**.52****	**.39****
Shifting Composite	-	-	-	-	-	**.54****
Updating Composite	-	-	-	-	-	-

Table 12. Study 2. Summary of brain regions that exhibited relationships with depressive symptoms.

I. T1 Depressive Symptoms No significant results						
II. T1 Depressive Symptoms, controlling for T1 Anxiety No significant results						
III. T2 Depressive Symptoms No significant results						
IV. T2 Depressive Symptoms, controlling for T1 Depression and Anxiety See table below						
Contrast	*Brain Regions*	*Volume (mm^3)*	*Max Z*	*MNI Coordinates of Peak Voxel (mm)* X	Y	Z
Valence (Pos < Neg)	**R. Middle Frontal Gyrus** (BA 8/46, DLPFC)	723	3.78	37	23	39
	R. Frontal Pole (BA 10)	556	4.59	21	55	13
	R. Frontal Orbital Cortex (BA 47, vlPFC)	180	3.86	45	23	-17
	L. Cingulate Gyrus, Anterior Division/ Paracingulate Gyrus (BA 32, rACC)	82	3.49	-11	49	1
	Medial Frontal Pole (BA 11, OFC)	73	3.29	5	55	-15
	Paracingulate Gyrus (BA 8)	71	3.23	5	33	35
	Cingulate Gyrus, Anterior Division (BA 24, dACC)	34	3.15	3	17	23
	L. Superior Frontal Gyrus (BA 8, SEF)	33	3.36	-7	27	57
	Cingulate Gyrus, Anterior Division (BA 24, dACC, MCC)	33	3.26	-1	-5	31
	Superior Frontal Gyrus (BA 6, SMA)	31	3.83	-5	15	57
	Paracingulate Gyrus (BA 8, pre-SMA)	30	3.52	1	21	47
	R. Frontal Orbital Cortex (BA 11, vmPFC)	25	3.33	13	9	-19
	R. Inferior Frontal Gyrus, pars triangularis (BA 45)	24	3.13	55	29	3
	Cingulate Gyrus, Anterior Division (BA 32, dACC)	22	3.20	1	11	37
Arousal (Pos + Neg/ 2 < Neu)	**R. Superior Frontal Gyrus/Middle Frontal Gyrus** (BA 8/9, DLPFC)	151	4.38	21	31	45

Table 12. Continued

Positive Affect (Pos < Neu)	**R. Middle Frontal Gyrus** (BA 8/9, DLPFC)	923	4.46	29	35	49
	Frontal Medial Cortex (BA 10/11, vmPFC)	184	3.38	-11	45	-11
	R. Frontal Pole (BA 10)	142	3.29	45	43	23
	L. Middle Frontal Gyrus (BA 9, DLPFC)	129	4.45	-27	31	43
	L. Superior Frontal Gyrus (BA 9, dmPFC)	128	3.68	-9	49	25
	Superior Frontal Gyrus (BA 8, SEF)	92	3.47	-9	21	49
	R. Superior Frontal Gyrus (BA 6, premotor cortex)	84	3.52	23	1	61
	R. Frontal Pole (BA 10)	71	3.32	45	51	-9
	R. Frontal Medial Cortex (BA 11, OFC)	65	3.78	9	39	-9
	L. Frontal Pole (BA 9)	61	3.15	-19	47	45
	Superior Frontal Gyrus (BA 9, dmPFC)	57	3.23	5	49	35
	L. Frontal Pole (BA 10/46, DLPFC)	39	3.15	-31	49	31
	R. Precentral Gyrus (BA 6)	37	3.11	15	-17	75
	R. Frontal Orbital Cortex (BA 47)	36	3.43	41	27	-5
	R. Middle Frontal Gyrus (BA 44)	22	3.10	39	15	33
	R. Middle Frontal Gyrus (BA 6)	21	3.34	39	3	41
Negative Affect (Neg < Neu)	No significant results					

Table 13. Study 2. Summary of Diagnostic and Statistical Manual of Mental Disorders Fifth Edition Diagnoses Based on the SCID (Structured Clinical Interview for the DSM).

Lifetime History N=47	**# of Lifetime Diagnoses**
Past MDD, N=6 Bipolar I, Current MDE, N=1 Specific Phobia, N=3 Social Phobia, N=4 Panic Disorder, N=1 GAD, N=3 PTSD, N=1 OCD, N=3 Past Alcohol Abuse, N=6 Past Alcohol Dependence, N=3 Past Substance Abuse, N=2	0 Disorders = 28 1, N=10 2, N=6 3, N=1 4, N=2 ≥1 disorder: N=19 (40%)
MDD = Major Depressive Disorder; GAD = Generalized Anxiety Disorder; PTSD = Posttraumatic Stress Disorder; OCD = Obsessive Compulsive Disorder	

FIGURES

Figure 1. Flow-chart depicting the procedures for Study 1.

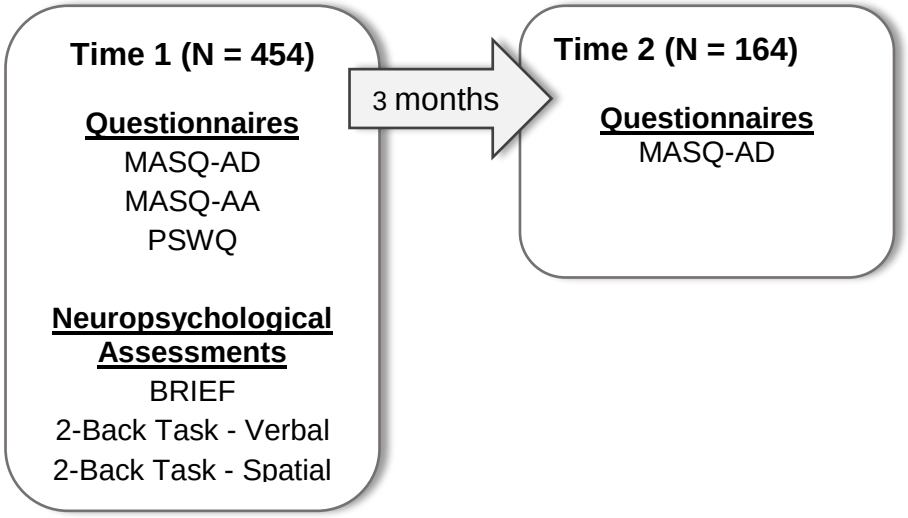


Figure 2. Flow-chart depicting the procedures for Study 2.

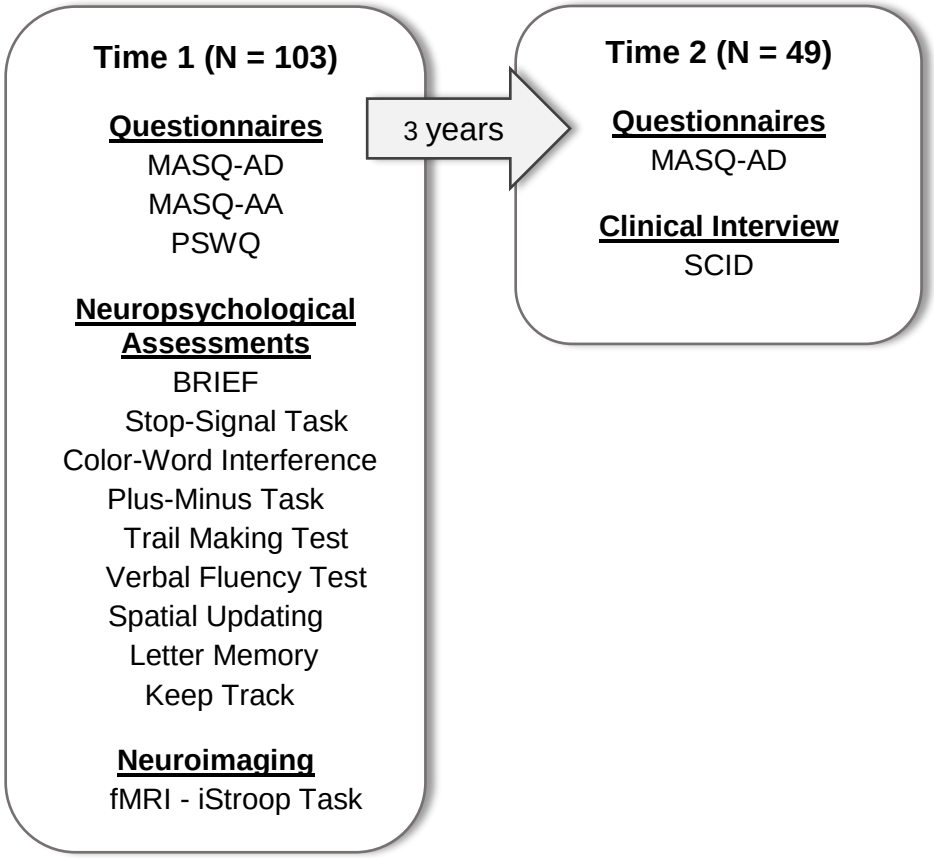


Figure 3. Schematic representation of a trial from the iStroop task. This diagram was reported in Infantolino et al. (unpublished manuscript).

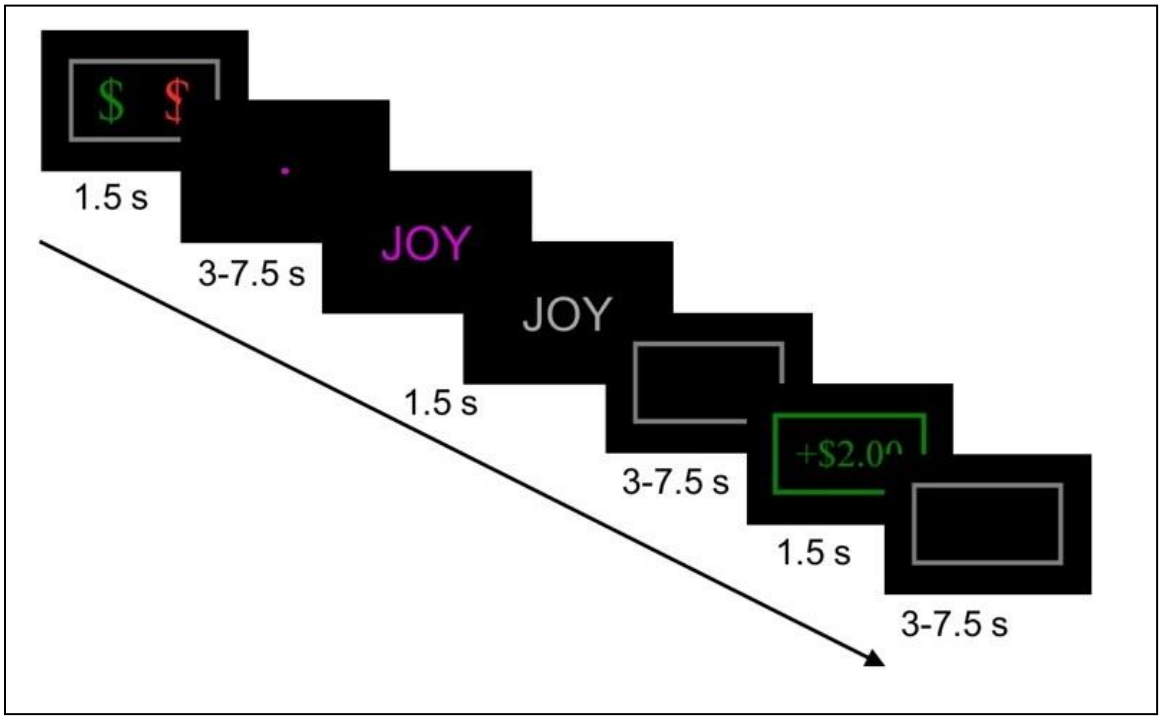
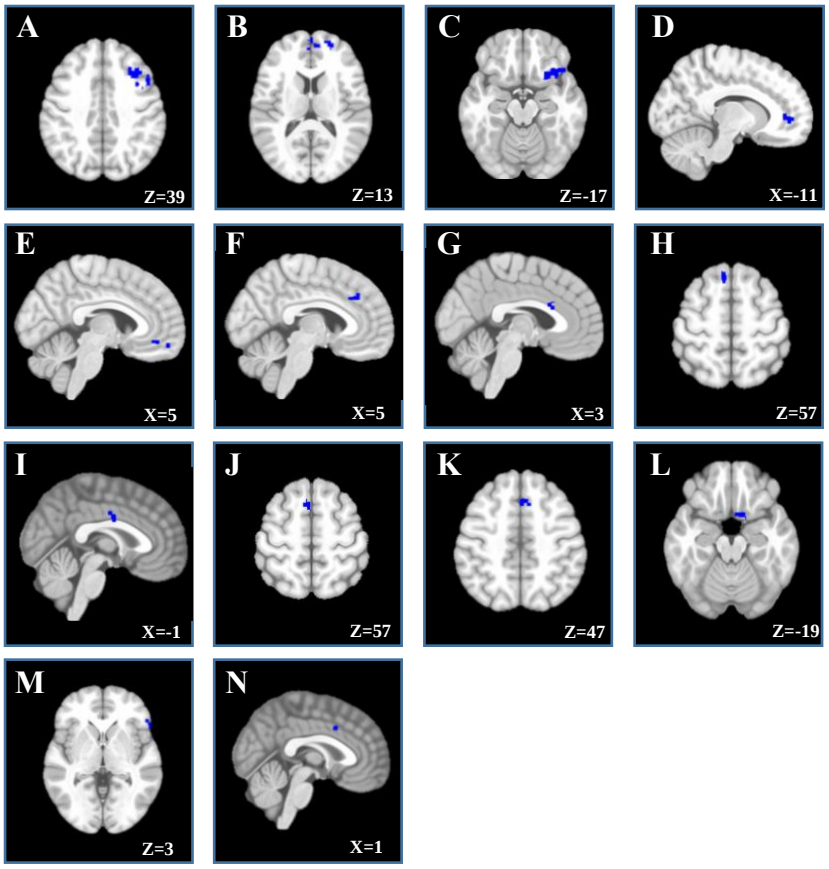
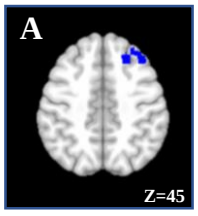


Figure 4. Study 2. Valence contrast. Areas of activation associated with depressive symptoms at T2 controlling for baseline symptoms of depression and anxiety.



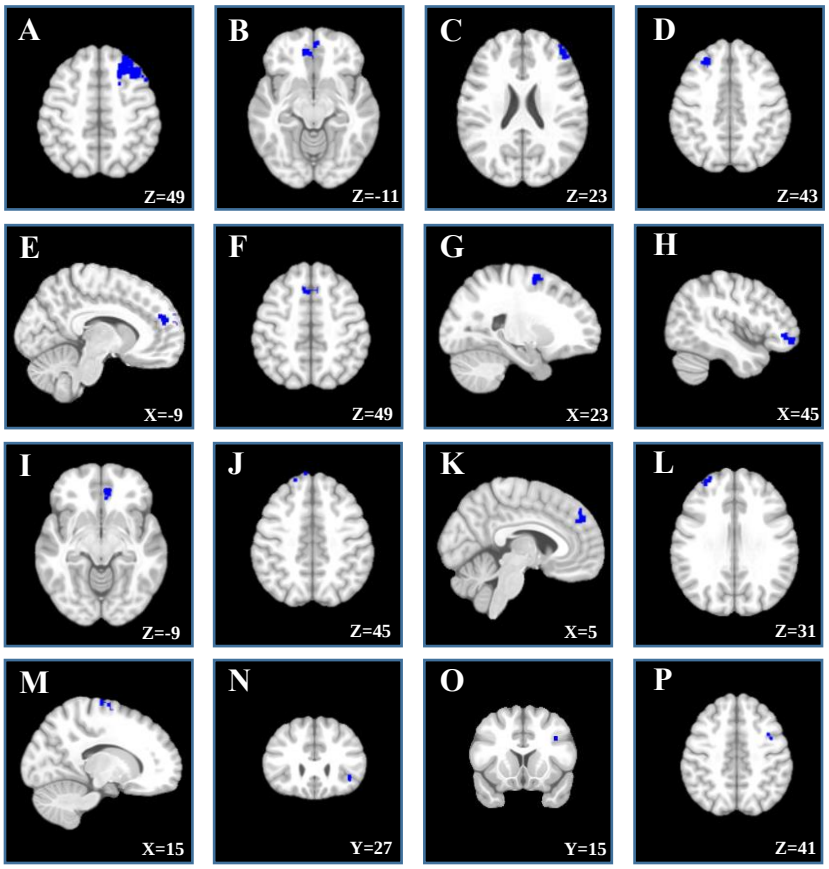
R = right. **(A)** R. Middle Frontal Gyrus, **(B)** R. Frontal Pole, **(C)** R. Frontal Orbital Cortex, **(D)** L. Cingulate Gyrus, Anterior Division/Paracingulate Gyrus, **(E)** Medial Frontal Pole, **(F)** Paracingulate Gyrus, **(G)** Cingulate Gyrus, Anterior Division, **(H)** L. Superior Frontal Gyrus, **(I)** Cingulate Gyrus, Anterior Division, **(J)** Superior Frontal Gyrus, **(K)** Paracingulate Gyrus, **(L)** R. Frontal Orbital Cortex, **(M)** R. Inferior Frontal Gyrus, pars triangularis, **(N)** Cingulate Gyrus, Anterior Division.

Figure 5. Study 2. Arousal contrast. Areas of activation associated with depressive symptoms at T2 controlling for baseline symptoms of depression and anxiety.



R = right. **(A)** R. Superior Frontal Gyrus/Middle Frontal Gyrus.

Figure 6. Study 2. PA contrast. Areas of activation associated with depressive symptoms at T2 controlling for baseline symptoms of depression and anxiety.



R = right. **(A)** R. Middle Frontal Gyrus, **(B)** Frontal Medial Cortex, **(C)** R. Frontal Pole, **(D)** L. Middle Frontal Gyrus, **(E)** L. Superior Frontal Gyrus, **(F)** Superior Frontal Gyrus, **(G)** R. Superior Frontal Gyrus, **(H)** R. Frontal Pole, **(I)** R. Frontal Medial Cortex, **(J)** L. Frontal Pole, **(K)** Superior Frontal Gyrus, **(L)** L. Frontal Pole, **(M)** R. Precentral Gyrus, **(N)** R. Frontal Orbital Cortex, **(O)** R. Middle Frontal Gyrus, **(P)** R. Middle Frontal Gyrus.

Figure 7. Study 2. Relationship between dACC activity and RT for the valence contrast at time 1.

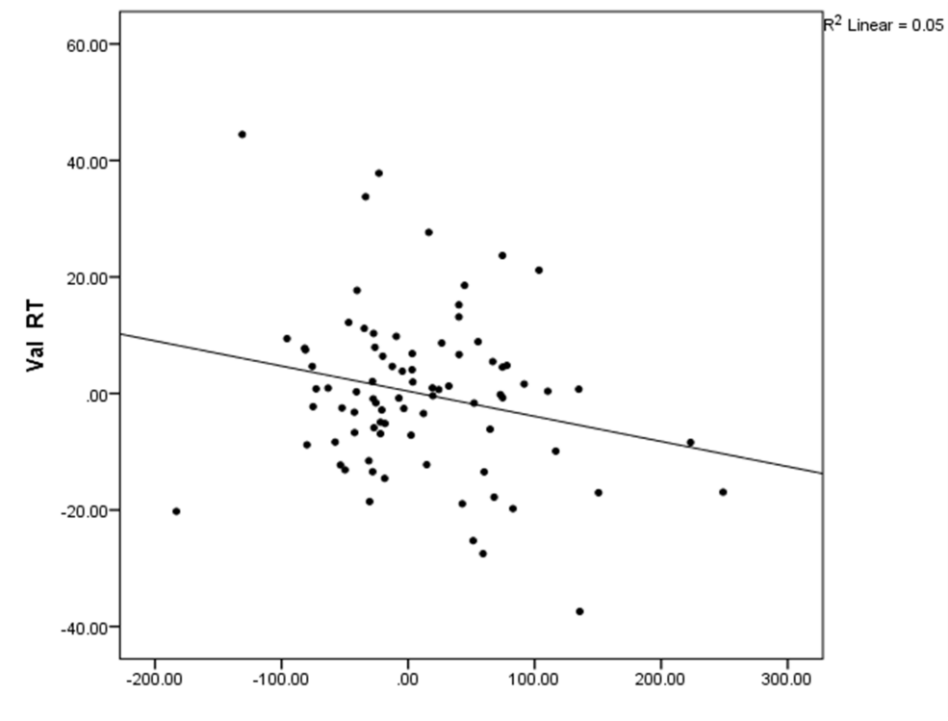
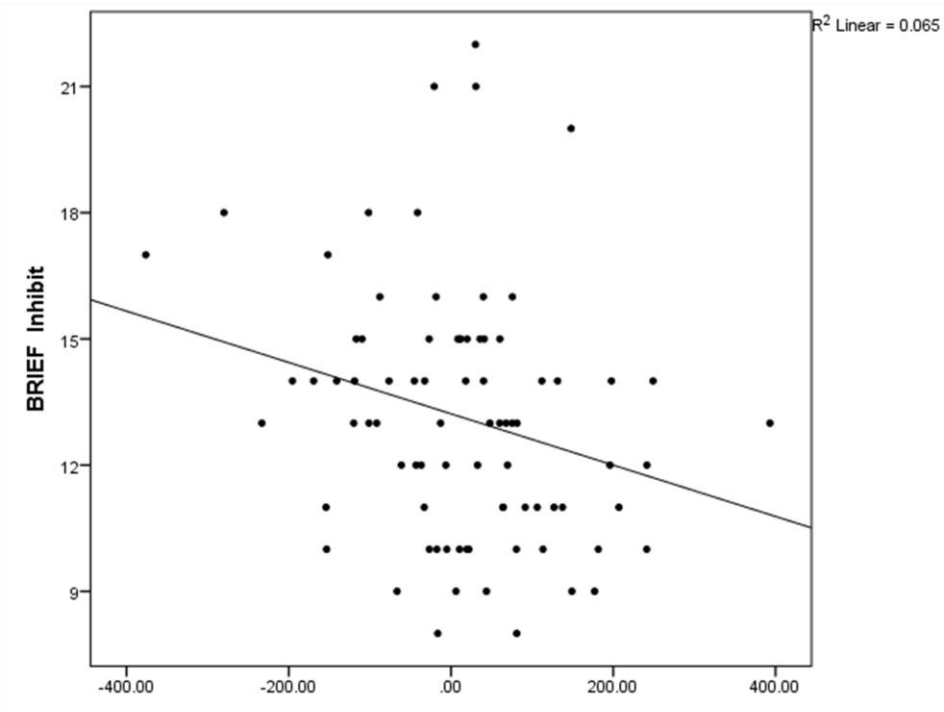


Figure 8. Study 2. Relationship between right vmPFC activity and BRIEF Inhibition scores at time 1.



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